Prospective studies are under way trying to identify red cell preparations without a detrimental effect on prognosis. However, as Tartter points out [3], evidence from the laboratory indicates that both red cells and red cell components are associated with immunosuppression. On the more comprehensive problem, whether any kind of blood transfusion reduces survival, randomized studies, despite their statistical attractiveness, are hardly ethically and practically feasible: both to transfuse patients without any indication and/or to withhold necessary transfusions would be unacceptable. As a consequence, analyses of retrospective series are the main source of human data on the prognostic effect of blood transfusion. Such analyses involve potential problems with what Mosteller and Tukey [34] call proxy variables, that is, variables reaching statistical significance in the model, despite the lack of causality between these variables and the response variable, because they act as stand-in for other variables not available in deriving the model. Suggestions are abundant in the literature that blood transfusion could be a proxy variable for a number of other parameters, generally not controlled for in the previously published analyses, all of which would be associated with a poor prognosis: advanced stage of disease, technically difficult surgery, prolonged operations, anemia, and the skill of the surgeon. Except for the last of these, such parameters may be considered as resulting from, rather than causing in themselves, a poor prognosis. Thus multivariate prognostic models may indirectly correct for these aspects provided that the model represents a sufficiently detailed description of prognosis as a function of clinico-pathological characteristics.

CONCLUSION

A detrimental effect of whole blood transfusion after cancer surgery was sought for in two relatively homogeneous groups with radically operated Dukes' B and C tumors, respectively. Although such an effect was evident when univariate statistical methods were used, this effect was explained by the uneven distribution of established prognostic factors among groups receiving none, moderate or massive whole blood transfusions. This study illustrates the importance of correcting for other prognostic factors when searching for an effect of blood transfusions on survival in retrospective series.

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Adjuvant Chemotherapy for Medulloblastoma: the First Multi-centre Control Trial of the International Society of Paediatric Oncology (SIOP I)

D.M. Tait, H. Thornton-Jones, H.J.G. Bloom,* J. Lemerle and P. Morris-Jones

Two hundred and eighty-six patients with medulloblastoma from 46 centres in 15 countries were treated in a prospective randomized trial designed to assess the value of adjuvant chemotherapy. All patients were treated by craniospinal irradiation. Those randomly allocated to receive adjuvant chemotherapy were given vincristine during irradiation and maintenance CCNU and vincristine, given in 6-weekly cycles, for 1 year.

The overall survival was 53% at 5 years and 45% at 10 years. At the close of the trial in 1979, the difference between the disease-free survival rate for the chemotherapy and control groups was statistically significant ($P = 0.005$). Since then, late relapses have occurred in the chemotherapy arm and the statistically significant difference between the two groups has been lost. Although there is now no statistical difference between the two arms of the trial, a benefit for chemotherapy persists in a number of sub-groups; partial or sub-total surgery ($P = 0.007$), brainstem involvement ($P = 0.001$), and stage T3 and T4 disease ($P = 0.002$). A number of prognostic factors for medulloblastoma have emerged; sub-total resection, extent of disease and being male sex carry a poor prognosis.

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In 1975, the International Society of Paediatric Oncology (SIOP) Brain Tumour Committee initiated a multi-centre randomized trial to determine whether adjuvant chemotherapy improved the survival rates of children with medulloblastoma and high-grade ependymoma treated by surgery and post-operative craniospinal (CNS) irradiation. At that time, reports of survival in medulloblastoma varied widely, with the best results showing survival rates of approximately 40% at 5 years and 30% at 10 years. Further improvement in survival was not anticipated without the introduction of chemotherapy, since it was considered that neurosurgery and radiotherapy were at the limit of normal tissue tolerance [1]. However, subsequent experience reported that more radical conventional treatment could improve survival rates to between 50 and 60% at 5 years [2, 3].

At the time the SIOP trial was designed, chemotherapy activity in brain tumours had already been documented with vincristine (VCR) [4–7]; 3-bis(2-choloroethyl)-1-nitrosourea (BCNU) [8, 9]; 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) [10–12]; methotrexate [13–16]. The SIOP trial elected to employ vincristine and CCNU delivered during and following surgery and radiotherapy (Fig. 1). The feasibility of the approach was tested in a pilot study conducted at The Royal Marsden Hospital. In this study, 40 children given CCNU and vincristine for medulloblastoma showed a highly significant improvement in survival at 5 years when compared with historical controls (70 vs. 32%, $P < 0.0001$) [17].

STUDY DESIGN

Patient eligibility

Criteria for eligibility were: age less than 16 years and a previously untreated histologically verified cerebellar medulloblastoma or a high-grade (Kernohan grades 3 and 4) intracranial ependymoma, arising either supratentorily or infratentorily. Eligible patients had undergone a major surgical resection of tumour and made a satisfactory post-operative recovery, with radiotherapy commencing within 1 month of surgery.

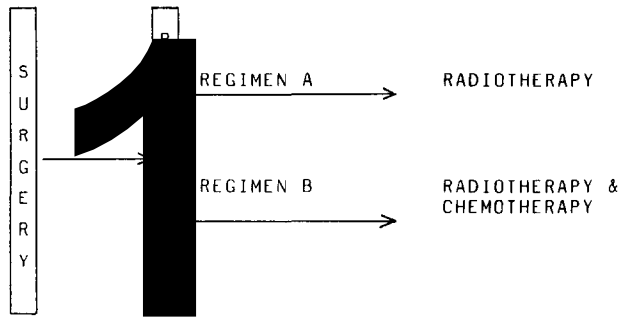

Fig. 1. SIOP I—medulloblastoma and ependymoma—trial design.

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*Professor H.J.G. Bloom of The Royal Marsden Hospital, who was instrumental in initiating this trial and was responsible for collection and collation of the data, died on 21st December 1988.

Pre-surgical assessment

Pre-surgical patient assessment to establish the presence of a posterior fossa mass varied over the years of the study. In the early years encephalography was commonly used, whereas towards the end of the study CT examination was usual. Assessment of the extent of tumour spread by examination of the cerebrospinal fluid (CSF) and myelography was advised but not mandatory.

Surgery

Surgical resection was as radical as possible without undue risk to life and function. It was recommended that ventriculo-atrial and ventriculo-peritoneal shunts should be avoided if possible.

Where necessary, steroids were used to control raised intracranial pressure, but were discontinued as soon as possible. Unstained histological sections of tumour were sent for central review.

Radiotherapy

Whole craniospinal, megavoltage or cobalt-60 radiotherapy was started as soon as possible following post-operative recovery. The protocol maximum tumour dose to the posterior fossa was 50–55 Gy with 35–45 Gy to the remainder of the brain in 7–8 weeks. The spinal cord dose was 30–35 Gy in 5–6 weeks. Treatment was daily, 5 days per week (Monday to Friday). In children under 2 years of age, the dose was reduced to 40–45 Gy to the posterior fossa with 30–35 Gy to the rest of the brain in 6–7 weeks and 30 Gy to the cord in 6 weeks.

Radiotherapy details were available in 260 of the 282 (92%) children with medulloblastoma [18]. No matter how great the protocol violation, no case was excluded from the analysis.

Chemotherapy

Vincristine and CCNU was randomly allocated to 164 patients with medulloblastoma or high-grade ependymoma. Vincristine was given by weekly injection (1 mg/m^2) during radiotherapy and both drugs being given for eight courses of maintenance treatment commencing 1 month after completing irradiation (Fig. 2). Courses were cycled every 6 weeks for 1 year and consisted of oral CCNU (100 mg/m^2 on day 1) and intravenous vincristine (1.5 mg/m^2 on days 1, 8 and 15).

Chemotherapy details were available for analysis in 110 of the 141 medulloblastoma patients randomized at treatment. The results of this analysis have been previously published [18].

Clinical endpoints

The purpose of the trial was to determine whether adjuvant chemotherapy improved survival rates in children with medulloblastoma or high-grade ependymoma treated by surgery and post-operative whole CNS irradiation. All results reported here refer to disease-free survival based on the log-rank test [19]. Tumour relapse had to be firmly established either by scintiscan, CT scan, CSF cytology or, if necessary, biopsy. Recommendations for treatment of relapse were given. For children who had not previously received chemotherapy, limited re-irradiation to the site or sites of tumour recurrence (30–35 Gray in 4–5 weeks) was recommended in conjunction with the trial chemotherapy protocol. Patients relapsing after adjuvant chemotherapy were recommended to receive limited re-irradiation with the decision regarding adjuvant chemotherapy left to the individual clinician in charge.

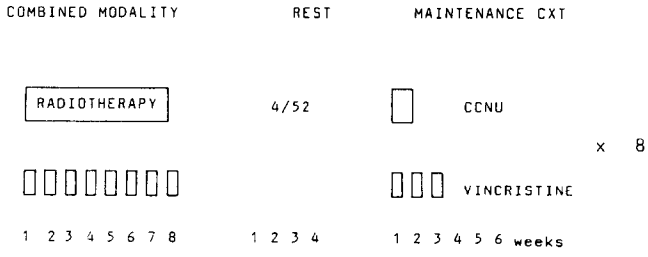

Fig. 2. SIOP I—combined chemo-radiation treatment schedule.

Statistical considerations

The randomization was stratified according to age group, sex and extent of surgery since previous experience showed these to be major prognostic factors. However, it is accepted that, since the youngest age group (children aged under 2 years at diagnosis) was scheduled in this protocol to receive a lower dose of radiotherapy, age group and radiotherapy dose are difficult to interpret.

Analysis of survival data, from time of operation, was carried out strictly according to the original case randomization. There have been no exclusions due to ineligibility after histological review, failure to carry out the randomized treatment or any protocol deviations. Of the patients with medulloblastoma, 141 were randomized to receive adjuvant chemotherapy during irradiation and subsequently as maintenance treatment, and 145 to receive no chemotherapy. Only one patient was entirely lost to follow-up, leaving 286 children for analysis. There were 208 boys (73%) and 78 girls (27%). Twenty-six children (9.1%) were under the age of 2 years at the time of treatment, 191 (66.7%) were between 2 and 9 years, and 69 (24.2%) were between 10 and 15 years.

Completeness of data collection

Pathology slides were received and reviewed from all but four of the 286 (1%) medulloblastoma patients. Collection of data regarding surgical and radiotherapeutic details was complete in all but five and three respectively of the 286 patients. Chemotherapy details were supplied for all but four of the 141 (3%) patients randomized to the chemotherapy arm.

Follow-up details were requested from participating centres on a yearly basis. For those reported to be dead (125), follow-up is obviously complete. For the remainder, 15% were lost to follow-up by 5 years and 66% by 9 years. There is no difference in the length of follow-up between the chemotherapy and control arms of the trial.

RESULTS

The trial opened in 1975. Over the subsequent 5 years, 44 centres from 15 different countries entered 286 children with medulloblastoma and 45 children with ependymoma. The 286 children with medulloblastoma are the subject of this paper; the results of treatment in the patients with ependymoma will be reported elsewhere. A list of participating centres and principal coordinators is given in Appendix I. By September 1979, the difference between the disease-free survival rate for chemotherapy and control groups of children with medulloblastoma reached a statistically significant level ($P = 0.005$) and the trial was closed to further case-entry since it was considered unethical to proceed.

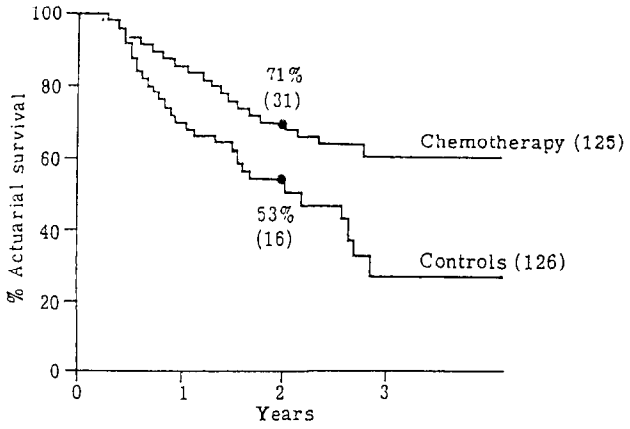

Fig. 3. Disease-free survival by treatment arm in 1979.

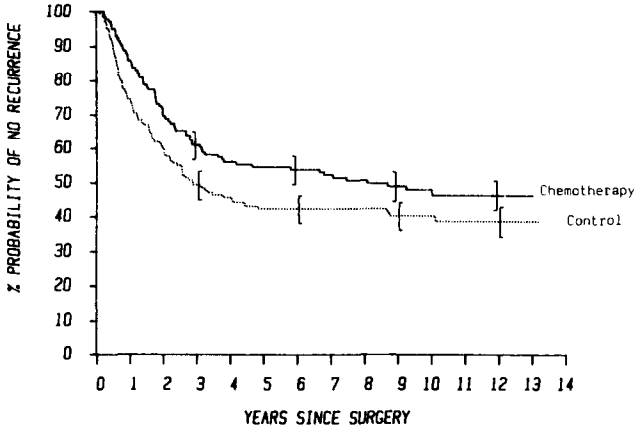

Fig. 4. Disease-free survival by treatment arm.

Survival

The 5-year overall and disease-free survival rates (time to disease recurrence or death from other cause), for all children with medulloblastoma were 53% and 48% respectively.

By 1979, there was a highly significant difference in disease-free survival in favour of chemotherapy, between the two arms of the trial ($P = 0.005$) (Fig. 3). With subsequent follow-up, more late relapses occurred in the chemotherapy arm; nine patients relapsed more than 5 years from surgery compared with three patients in the control arm. As a result, the difference between the two arms in disease-free survival has declined over the years, and at last follow-up (1988) was only of borderline significance ($P = 0.07$) (Fig. 4). However, an advantage for chemotherapy has persisted in some patient sub-groups.

Prognostic factors

A number of prognostic factors have been examined; several have emerged as strong predictors of survival (Table 1).

T-stage. T-stage proved to be a very strong predictor of outcome. The 113 patients with early stage disease (T1, T2) had a 64.6% disease-free survival at 5 years, as compared with 38.0% in the 163 patients with advanced disease (T3, T4) ($P < 0.005$).

Table 1

Groups	% 5 year survival	Significance
Brainstem involved	41.4	NS
Brainstem not involved	51.7	
Biopsy/partial surgery	33.3	
Subtotal surgery	52.1)	
Total surgery	50.8)	$P < 0.05$
T1 and T2 tumours	64.6	
T3 and T4 tumours	38.0	$P < 0.005$
Age < 2	38.5	
Age 2–9	50.2	
Age 10+	47.0	NS
Male	44.6	
Female	58.4	$P < 0.025$
Major centre	56.9	
Minor centre	41.8	$P < 0.005$

Extent of surgery. From the early years of analysis, patients undergoing total (128) or sub-total (111) excision have tended to do better than those in whom only a partial excision (39) could be performed. The extent of the difference in disease-free survival has fluctuated from year to year and at present shows borderline significance ($P < 0.05$).

Size of participating centre. Centres were designated as 'major' if they had entered 20 or more patients into the trial. One hundred and twenty-four patients were treated in major centres and these patients had a significantly better disease-free survival ($P < 0.005$) than the 162 patients treated at other centres.

Sex. Disease-free survival in girls was better than in boys ($P = 0.012$), the 10-year survival rates being 57 and 40% respectively ($P < 0.025$).

Age. Although patients in the youngest age group (< 2 years) appeared to do worst, it must be borne in mind that age and radiotherapy dose are confounded in the trial, with the youngest children receiving a lower dose of radiation.

Brain stem involvement did not appear to predict for disease-free survival independently, the 94 children with brainstem involvement having a similar probability of recurrence to the 174 children without brainstem disease.

Prognostic factors and type of treatment

Sub-group analysis was performed to examine the possibility of interaction between tumour/patient characteristics and treatment. A large effect was seen in a few sub-groups.

Brainstem involvement. Of the 94 patients with brainstem involvement, 48 were randomized to the chemotherapy arm and 46 to the control group. Those who received chemotherapy had a significantly better disease-free survival ($P < 0.005$), a difference which has persisted throughout the years of follow-up (Fig. 5).

T-stage. For the 113 patients with early stage disease (T1 and T2), chemotherapy had no effect on disease-free survival. However, with advanced disease (T3 and T4), the 91 patients who received chemotherapy had a significantly better disease-free survival ($P = 0.002$) than the 72 control patients (Fig. 6).

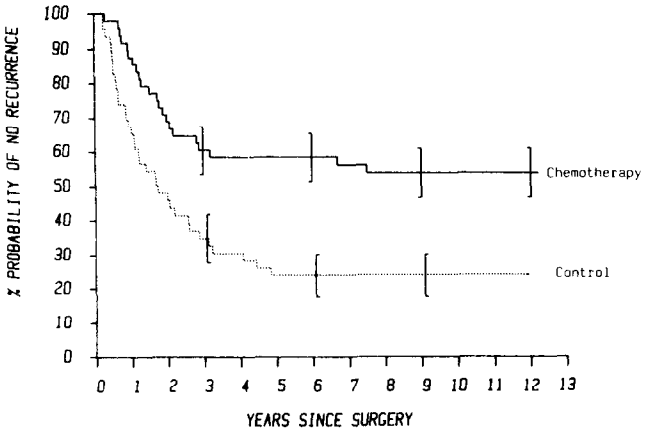

Fig. 5. Disease-free survival in patients with brainstem involvement by treatment arm.

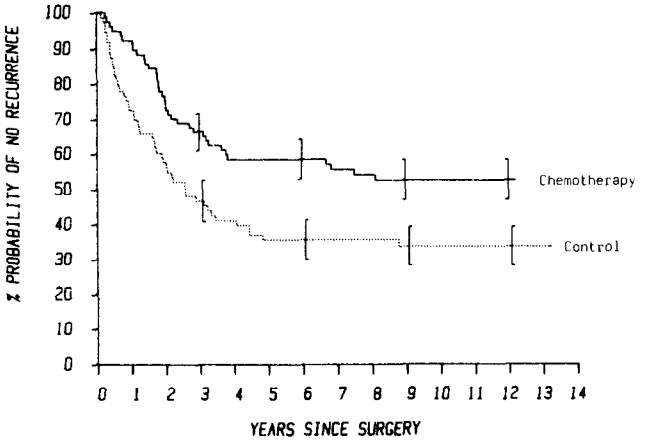

Fig. 7. Disease-free survival in patients undergoing partial surgery by treatment arm.

Extent of surgery. In the 128 patients who had undergone total resection, there was no tendency for chemotherapy to improve survival. However, a positive effect for chemotherapy was detected in those children whose resection was either partial or subtotal ($P < 0.01$) (Fig. 7).

Toxicity

Details of acute toxicity and its influence on treatment delivery have been previously reported [18]. Of the four non-tumour deaths in the chemotherapy arm, there was one patient in whom chemotherapy could have contributed to death. This was a 3-year-old boy in whom there was a protocol error with delivery of maintenance chemotherapy for 2 years instead of the specified 1 year period.

Two patients have developed a second malignancy, neither of whom received adjuvant chemotherapy. In one a meningioma occurred within the area of the posterior fossa boost 9 years after treatment. The other developed a soft tissue mass in the occipital region after 10 years which histologically was classified as a low grade sarcoma. So far both patients remain alive after local surgery only. There have been no reported cases of leukaemia in the follow-up period.

DISCUSSION

Randomized trials in rare tumours, such as medulloblastoma and ependymoma, require multi-centre collaboration. Despite this, it may take many years to accrue the necessary patient numbers.

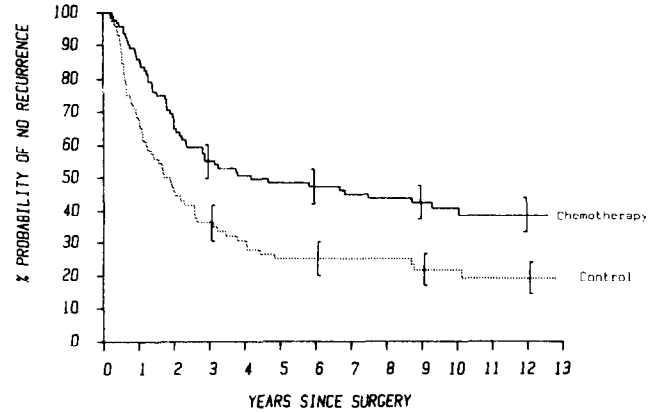

Fig. 6. Disease-free survival in patients with advanced stage disease (T3 and T4) by treatment arm.

Although multi-centre trials have proved useful in advancing the management of rare childhood tumours, experience has demonstrated inherent problems in this form of research. Variation between centres, in terms of number of referrals, clinical experience, facilities and resources available for treatment, mean that protocol deviations are inevitable.

Maintenance of motivation among geographically dispersed centres over a prolonged period, particularly where the initial level of commitment of each centre may have differed appreciably, is difficult. As a result, data collection and follow-up may be incomplete. This is compounded by issues of confidentiality to which some European countries are particularly sensitive. These issues may become more pertinent when the care of children in the trial is taken over by a clinician unfamiliar with the trial, as is often the case with the approach of adulthood.

A project of this magnitude inevitably represents a long-term commitment, and there is an inescapable loss of timeliness in that many of the issues being explored may no longer be relevant. This has been one of the major criticisms of the SIOP I study; by the time the analysis was underway the chemotherapy used and its scheduling was no longer considered optimal. However, when the trial was designed in the early 1970s, the introduction of combination chemotherapy during and following craniospinal irradiation was considered to be a radical approach. The results and criticisms of this trial had a major influence on the design of the second SIOP medulloblastoma trial in which the effect of giving a more intensive module of chemotherapy between surgery and radiotherapy was tested. However, preliminary results suggest that this approach has failed to exhibit a chemotherapy benefit [20]. As regards the design of future studies, the range of single chemotherapeutic agents with demonstrable activity in medulloblastoma is now much expanded and includes cisplatinum [21, 22], carboplatin [23, 24], cyclophosphamide [25] and ifosphamide [26]. As yet there are no data for etoposide as a single agent, or for methotrexate in adequate dosage for CNS penetration. The combination of vincristine, *cis*-platinum and CCNU [27], and of vincristine and cyclophosphamide [28] have produced encouraging results in phase II studies.

Despite the shortcomings outlined, multi-cultural studies of this type also have indisputable strengths. In particular, it can be argued that implementing a treatment protocol over a wider range of clinical settings, with very different resources at their disposal, is a far better indicator of future efficacy than a protocol tested in a single centre. Nor should one overlook the benefits

to patients being treated in smaller centres where adherence to a protocol may improve overall management [29].

The aim of this trial was to examine the effectiveness of chemotherapy, and therefore the single planned comparison was that between the chemotherapy and control arms. This comparison is thus of major importance and will be considered first; other findings, being incidental, will be considered separately.

As patients accrued and the trial matured, the difference between the chemotherapy and control arms became large and significant, until in 1979, 5 years into the trial with 286 medulloblastoma patients entered, the difference was such that it was considered unethical to deprive patients of chemotherapy. The trial was therefore closed at this stage. In subsequent years, however, the difference between the two groups has diminished and no longer achieves a conventional level of significance.

The reason for the instability of the difference was initially unclear. It is true that the trial was closed before patient accrual had allowed for the commonly accepted 80% power to detect a difference significant at the 5% level, for which some 350 patients would have been needed. However, it is also accepted that the size of the observed difference at that time was sufficient to render the conduct of the trial along the previously agreed lines not feasible. Whether or not it was right to terminate the trial at that time may well remain in dispute. However, the subsequent diminution of the difference between chemotherapy and control groups, due to late treatment failures in the patients who received chemotherapy, demonstrates an effect of chemotherapy in terms of growth delay. The decision to terminate the trial at an early stage is vindicated by the real but transient effect of chemotherapy which did not contribute to cure.

The prognostic factors, brainstem involvement, extent of surgery and T-stage, are inter-related. However, there were problems with definition of clinical status and subsequent allocation to sub-groups. For example, of the 94 patients described as having brainstem involvement, 18 were reported as having had total removal of tumour, which seems unlikely. Because of the uncertainty associated with this part of the data, a detailed analysis of the independence of these prognostic factors has not been performed.

The apparently better results achieved in the major centres may represent a greater intensity of treatment, not only in terms of extent of surgery, but also in willingness to deliver radiotherapy and chemotherapy despite acute toxicity, particularly myelosuppression.

The proportion of males in this trial (74.2%) was higher than that found in a North American trial conducted over a similar period (64.7%) [30]. In part, this may result from the population of international and tertiary referrals in the European study, particularly to the larger centres which tended to include more male children. The exception was the Institut Gustave-Roussy where equal numbers of boys and girls were entered. The non-European origin of a proportion of male patients may have contributed to the fact that girls had a statistically better disease-free survival compared with boys.

The analyses of the effect of chemotherapy in subgroups were unplanned; had the planned comparison been highly significant, far less credence would have been placed on the result of the subgroup analyses. It is recognised that, when performing unplanned analyses in sub-groups, the type I error rate is likely to be high, and adjustments to the nominal significance level should be made to allow for this. Moreover, when simulations to estimate the true significance levels were performed on the data from this trial [31], even the adjustments recommended by standard statistical theory overestimated the significance levels in subgroups where the planned comparison is of marginal significance, as it is here. In other words, despite the size of the differences between treatment arms in some of the sub-groups, the interpretation of this is far from clear cut and critical examination is warranted. For example, it is difficult to envisage the mechanism whereby chemotherapy would have such a large effect in certain sub-groups, such as brainstem positive and advanced T-stage, but have no effect in the less severely affected counterparts, brainstem negative and early T-stage. Although the magnitude of effect might be variable for certain circumstances, the trend would be expected to be in the same direction. Furthermore, in tumours where adjuvant chemotherapy has shown an effect on disease-free survival, this is usually most evident where tumour load is minimal. However, the finding of a similar trend in sub-group analysis in the Children's Cancer Study Group (CCSG) study could arguably give strength to the SIOP result [30]. This North American study using CCNU, vincristine and prednisolone has shown similar results to the present study with no significant difference in survival between the two treatment arms.

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APPENDIX 1

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