EDULLOBLASTOMA is the most common intracranial tumor in children, with an incidence of 0.5 per 100,000 children. Surveillance imaging is a major part of treatment in these children and the imaging frequency has important implications for anesthesia and radiology service provisions. The improvement in the 5-year survival time from 30% in the 1960s to current rates of 50 to 70%, which has been attributed to improvements in perioperative care, imaging, surgical techniques, chemotherapy, and radiotherapy, has resulted in longer survival times and an increase in the demand for follow-up imaging.

The value of surveillance imaging has been questioned by previous researchers. In the study conducted by Torres, et al., no child with recurrent medulloblastoma survived and the authors stated that surveillance imaging was of no value. Three studies have demonstrated that the majority of recurrences are detected on surveillance imaging and were unable to demonstrate improved survival in children with asymptomatic recurrences. Other studies have demonstrated that children in whom surveillance imaging detected recurrences survive longer than patients who present with symptomatic recurrences, but these studies have been limited by short follow-up periods and small numbers of children with recurrences. A single study, in which all tumor types were combined, demonstrated that the majority of recurrences are detected by the emergence of symptoms within the first 8 postoperative months and by surveillance imaging after 8 months, but was unable to show a significant improvement in overall survival in patients with surveillance imaging–detected recurrences.

Abbreviations used in this paper: CI = confidence interval; CSF = cerebrospinal fluid; CT = computerized tomography; MR = magnetic resonance.
Clinical Material and Methods

Data were obtained from the Department of Neurosurgery database of children with histologically confirmed posterior fossa medulloblastoma. Data were prospective-ly entered into this database from January 1987 to August 1998, allowing this study a minimum follow-up period of 3 years. The patient age at diagnosis, sex, histological characteristics of the tumor (classic or desmoplastic), time of first resection and extent of tumor clearance, and appearance of recurrences (date and number of recurrences as well as no-tations on whether they were symptomatic) were recorded by a retrospective review of the database and of all patients’ clinical notes. The available imaging and radiological re-port of all patients were retrospectively reviewed by a neu-roradiologist (D.E.S.). Discrepancies between observations by this neuroradiologist and the radiology reports were re-viewed by another neuroradiologist (W.K.C.).

During the study period, all children 3 years of age and older received craniospinal radiation therapy (final dose 50–55 Gy over a 6-week period). Before 1994, children older than 3 years of age were also given chemotherapy on a case-by-case basis, and after 1994, chemotherapy was given as part of a study or under a treatment protocol. From 1992 onward, patients younger than 3 years of age received the United Kingdom Children’s Cancer Study Group baby brain chemotherapy protocol. Before 1992, these patients received chemotherapy on a case-by-case basis. Details of patient treatment can be found in a previous paper from our institution by David and associates.1 Following each tumor recurrence, treatment was reviewed on an intention-to-treat basis; that is, the patient was considered to have received treatment if treatment commenced but was withdrawn when the patient was considered too ill to tolerate further treatment.

Imaging Studies

All patients who underwent imaging at our hospital were treated according to current oncology imaging protocols. The preoperative MR imaging (Magnetom, Vision, and Symphony; Siemens, Erlangen, Germany) protocol for the brain included axial T2-weighted, precontrast administra-tion coronal T1-weighted, and postcontrast administration T1-weighted images obtained in either two or three planes. Precontrast and postcontrast administration CT scans (model T60A; Toshiba Corp., Tokyo, Japan, and Somaton Plus-4 scanners; Siemens) were obtained in some children before MR imaging became routinely available. Preoperative imaging of the spine included contrast-enhanced sagittal and axial T1-weighted imaging through a suspected abnormal-ity. Myelograms were obtained in the early cases. The preferred postoperative imaging method was MR imaging, which was performed within 48 hours after surgery. Imme-diate postoperative imaging of the spine was performed for tumor staging, only if preoperative images had not been ac-quired. Cerebrospinal fluid collection for cytological ex-amination was not used as part of the protocols during the study period.

Surveillance images were defined as the images obtained following resolution of any postoperative complications. The exact timing of acquisition of these images was deter-mined by the treatment regimen, and the protocols currently in use were started in 1992. Cranial MR images were first acquired at 3 months, then every 6 months for 2 years and every 12 months thereafter, until a recurrence developed or the child was discharged from neurosurgical care (minimum 5 years). Earlier follow-up images (obtained every 2–3 months) were required in the event that the findings ap-peared equivocal. The frequency of surveillance imaging was calculated from the first surveillance image to the end of the 1st follow-up year and for each subsequent year until discharge from neurosurgical care or tumor recurrence oc-curred.

Spine imaging was included as part of the surveillance imaging studies only in children who had disseminated dis-ease at the time of diagnosis or in whom a recurrence was detected. (Children > 3 years of age receiving cyclophos-phamide, doxorubicin, vincristine, and prednisone [CHOP 455] underwent imaging [including spine imaging] at 41 and 60 weeks postoperatively, then every 2 years and every year thereafter.)

Definition of Terms

Macroscopic excision of the tumor was defined as no evidence of residual lesion on postoperative MR images. In patients in whom the postoperative study was a CT scan, macroscopic excision was defined as complete clearance described on the operative report and no evidence of tumor on the CT scan. Images were termed surveillance images if they were obtained independent of patient symptoms and were called symptom-prompted images if they were ob-tained to investigate new symptoms.

Statistical Analysis

Patients were followed up for variable lengths of time and, hence, Cox proportional hazard models were used to identify factors associated with time to recurrence, time to death, and time to death from first recurrence. Patients who died before a recurrence was identified were treated as censored in the time-to-recurrence model. The presence of metastases was recorded at referral. The presence of metastatic disease and whether recurrences were identi-fied by symptoms or by neuroimaging were entered into the models as time-varying covariates by using statistical software (EGRET version 1.02.10; Cytel Software, Cam-bridge, MA).

Results

Of the 111 children with posterior fossa medulloblas-tomas whose information was entered into the database be-tween January 1987 and August 1998, two children died within 1 month after surgery and two children were lost to follow-up review after they returned to Greece follow-ing surgery. The study group of the remaining 107 chil-dren consisted of 35 girls and 72 boys, with a mean age of 6 years and 3 months (range 2 months–15 years and 6 months). Approximately one half of the patients (53 pa-tients [49.5%]) experienced a recurrence. Details of the tu-mor resection, histological characteristics, and metastatic disease at presentation are shown in Table 1.

Surveillance Imaging

The surveillance images and/or written reports of their results were available for review in 98 (92%) of the 107 pa-
tients (363 imaging sessions; Table 2). Recurrence and clinical data from the remaining nine children were available from the neurosurgical database. Sixty-one children had undergone MR imaging of the spine and 45 myelography at presentation; one child did not undergo imaging of the spine at diagnosis.

During the course of the study, the imaging modality of choice changed from CT scanning to MR imaging. Computed tomography scanning was used for postoperative imaging in the majority of patients, in equal proportions in the recurrence (39 of 53 patients) and no recurrence (35 of 54 patients) groups. Operative notes were reviewed to distinguish complete from incomplete excision in these children. Magnetic resonance imaging alone was used to determine the extent of excision in those patients who had undergone postoperative MR imaging.

Surveillance imaging was performed using MR imaging in the majority of patients, in equal proportions in the recurrence (33 of 49 patients) and no recurrence (27 of 48 patients) groups. Eight children (four in each group) were followed up abroad and details on the imaging modalities in use were not available. One child in each group died before the first scheduled surveillance image could be obtained.

During the 1st follow-up year, surveillance imaging was performed at a median of every 4 months (range 1.5–11 months) and during subsequent years, at a median of every 10.3 months (range 3.6–27 months). There was no significant difference between mean and median intervals of surveillance imaging in the no recurrence, symptomatic recurrence, and asymptomatic recurrence groups. In one patient the imaging interval was 27 months; that child’s mother had decided that her child would not undergo imaging regularly during the follow-up period, but did agree to acquisition of an image prior to discharge from neurosurgical care, after 10 years of disease-free clinical surveillance. Surveillance imaging included the spine in 30% of studies performed during the 1st surveillance year and in 42% of studies performed during subsequent years, 37% overall.

### Tumor Recurrences

Fifty-three patients (mean age 6 years and 4 months, range 2 months–14 years and 3 months) experienced a total of 68 recurrences; 41 children had a single recurrence, nine had two recurrences, and three had three recurrences. Surveillance imaging revealed 10 (19%) of the 53 first recurrences and only 15 (22%) of all 68 recurrences. Clinical data concerning whether a recurrence was symptomatic or asymptomatic were not available for three recurrences. The timing and location of tumor recurrences are shown in Tables 3 and 4. Of 117 surveillance studies obtained in children with recurrences, 48 included the spine; on the basis of these studies, no child was found to have spinal tumor recurrence in the absence of cranial disease.

The median follow-up period in the 52 children who survived without recurrent disease was 5 years and 11 months (mean 5 years and 6 months, range 2 months–10 years and 6 months). The survival rate in the recurrence group was 22.6% (12 of 53 patients), and the median survival period was 4 years and 9 months (mean 5 years and 11 months, range 5 months–8 years). Only two of the 12 survivors, who originally presented while younger than 3 years of age, were subsequently eligible for radiotherapy when a recurrence was detected. The median survival of the 41 children with recurrent disease who died was 23 months. Once a single recurrence was detected, the survival rate among children in the surveillance imaging–detected recurrence group was 40% (four of 10 patients) and the rate in the symptomatic group was only 14.6% (six of 41 patients). The overall survival of the study group was 40% (Table 5).

Two children died before a recurrence developed. One child who had Fanconi anemia (Fragile X) and was unable to tolerate radiotherapy and chemotherapy died 2 months after diagnosis. The second child, who presented at 4 years and 4 months with a nonspecific illness and headache, died unexpectedly. A postmortem examination failed to reveal evidence of tumor recurrence. One child with disseminated
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**TABLE 3**

<table>
<thead>
<tr>
<th>No. of Recurrence</th>
<th>Image-Identified Recurrence</th>
<th>Time From Presentation to Recurrence (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st*</td>
<td>42</td>
<td>3 to 89, Median 15.5</td>
</tr>
<tr>
<td>2nd*†</td>
<td>6</td>
<td>3 to 108, Median 30</td>
</tr>
<tr>
<td>3rd†</td>
<td>2</td>
<td>4 to 114, Median 35</td>
</tr>
</tbody>
</table>

* Insufficient clinical data concerning whether the recurrence was symptomatic or asymptomatic were available in one child who had a first recurrence and in two children with a second recurrence.
† Includes data from nine children who experienced two recurrences and three children who had three recurrences.

Factors at Presentation Associated With Time to Recurrence, Time to Death, and Time to Death After Recurrence

Incomplete excision of tumor was associated with a significantly reduced time to recurrence (hazard ratio 1.73, 95% CI 1.01–2.97, p = 0.048) and time to death (hazard ratio 2.69, 95% CI 1.44–5.01, p = 0.002). Following a recurrence, although not statistically significant, incomplete—complete excision was associated with an increased risk of death (hazard ratio 1.93, 95% CI 0.96–3.87, p = 0.07).

Patient age at diagnosis, sex, and tumor histological findings were not significantly associated with time to recurrence, time to death, or time to death after a recurrence. The CIs for the histological characteristics of the tumor, however, were relatively wide because the number of children with desmoplastic medulloblastoma was small: six patients did not experience any recurrence and survived, and one patient in the recurrence group died 19 months after presentation.

The presence of metastatic disease at presentation was not significantly associated with a significantly increased time to recurrence (hazard ratio 1.39, 95% CI 0.74–2.55, p = 0.31), time to death (hazard ratio 1.16, 95% CI 0.55–2.42, p = 0.71), or time to death following recurrence (hazard ratio 1.18, 95% CI 0.53–2.62, p = 0.68). Thirteen children in the recurrence group had metastatic disease at the time of presentation, compared with eight in the nonrecurrence group. After accounting for completeness of excision, none of the other factors known at presentation became significant.

Symptomatic Compared With Asymptomatic Recurrence

When the first recurrence was identified on the basis of symptoms (42 patients), the children tended to survive for a shorter time (hazard ratio 3.72, 95% CI 1.42–9.76, p = 0.008) than children in whom the first recurrence was asymptomatic and detected by surveillance imaging (10 patients) (Fig. 1). Data regarding the type of relapse (symptomatic compared with asymptomatic) were not available in one child. The association remained after accounting for completeness of excision (hazard ratios, CIs, and probability values for excision and symptom identification, respectively: 2.43, 1.17–5.03, p = 0.017; and 4.54, 1.69–12.18, p = 0.002). When the recurrence was identified by symptom-prompted imaging patients lived a median time of 4 months after recurrence, whereas when it was identified using surveillance imaging patients lived a median of 17 months.

Factors During Illness Associated With Time to Recurrence, Time to Death, and Time to Death Following Recurrence

The number of recurrences was associated with a significantly reduced time to death (hazard ratio 2.22, 95% CI 1.69–2.92, p < 0.001). There was a strong association between the number of recurrences and the completeness of excision. The two variables were not independently associated with time to death.

Treatment Following Recurrence in the Symptomatic and Surveillance Imaging–Detected Groups

Treatment differences in the symptomatic and asymptomatic recurrence groups following a single recurrence are given in Table 6. Following a second recurrence one of four children in the asymptomatic group underwent additional surgery and two received etoposide for palliation. One of six children in the symptomatic group received radiotherapy. Following a third recurrence, all three children received etoposide as palliative chemotherapy.

**TABLE 5**

<table>
<thead>
<tr>
<th>No. of Recurrences</th>
<th>No. of Live Patients</th>
<th>No. of Dead Patients</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

* Overall survival in the recurrence group is 19%.

Discussion

This is the largest published study, with the longest fol-
low-up period, of childhood medulloblastoma. Recurrent disease occurred in 49% of the children, of whom 19% survived a median of 4 years and 9 months. We have demonstrated an improved length of survival in children with recurrent medulloblastoma that was detected by surveillance imaging.

The association between incomplete tumor excision and reduced time to death, time to recurrence, and time to death following a recurrence in children has been reported as one of the most significant variables affecting survival.1,3,10,11,17,24 but has not been associated with survival in other studies.1,7,13,15,23 The detection of incomplete resection by early postoperative MR imaging (performed in <72 hours) gives the neurosurgeon the chance to reoperate on residual disease prior to the institution of adjuvant therapy.

We did not demonstrate significant reductions in the time to death, time to recurrence, and time to death following recurrence in patients with metastatic disease at presentation. This is in agreement with the findings of a recent study in young children by Walter, et al.,26 but is at variance with the results of other studies1,7,13 which included many of the patients in the present study. This may reflect recent improvements in adjuvant therapy.

Relationship Between Identification of the First Tumor Recurrence and Outcome

How Effective is Surveillance Imaging? Surveillance imaging has previously been shown to be beneficial in three studies,12,20,27 two of which involved frequent surveillance imaging: every 3 months for 2 years and every 6 months thereafter.12,20 Two studies have shown surveillance imaging to be of possible benefit,18,22 whereas two others have shown it to be of no benefit.25,30 Asymptomatic recurrences in these studies accounted for between 17 and 83%; in our study surveillance imaging detected such recurrences in 19% of patients.

The risk of death at any given time is approximately 3.7-fold greater for patients whose recurrences are identified by symptom-prompted imaging than for those in whom recurrences are identified by surveillance imaging. To overcome lead-time bias—that is, the bias that recurrences are detected earlier on surveillance images and therefore benefit from earlier adjuvant therapy—the increased lifespan needs to be more than half the average time between the acquisition times of surveillance imaging. This addresses the following question: do patients live longer or is the recurrence just identified earlier? In our study, the median time from the first recurrence to death when the recurrence was asymptomatic was 17 months and 3 months when it was identified by the onset of symptoms. The median increase in lifespan in patients with surveillance imaging–identified recurrence was 13 months, which is more than half the median interval between neuroimaging sessions in the 1st year (half the median interval between imaging studies 2 months) and in subsequent years (half the median interval between imaging studies 5.1 months).

Although we tended to detect first recurrences earlier when they were accompanied by symptoms, there was no significant difference between the mean time of 20.7 months to the first recurrence in symptomatic patients (median 15.5 months, range 3–89 months) and the mean time of 23.5 months in asymptomatic patients (median 19.5 months, range 6–44 months).

How Often Should Surveillance Imaging be Performed? To choose optimal intervals for surveillance imaging, one needs to look at the interval between presentation and first recurrence and the interval between subsequent recurrences. The mean time to the first recurrence in patients within the 1st year was 8.2 months, with a median of 8 months (range 3–12 months); in subsequent years in 34 patients it was a mean of 29 months and a median of 25 months (range 13–89 months). The mean time between recurrences in 15 patients was 8.4 months, with a median of 8.8 months (range 1–19 months).

How Long Should Surveillance Imaging Continue to be Performed? The longest time that a child undergoing surveillance imaging remained tumor free was 7 years and 5 months; the child had presented with symptoms after having been discharged from neurosurgical care after a 5-year follow up. To identify all instances of tumor recurrence, routine surveillance imaging would have to be continued.

![Graph showing survival curves in 50 of 53 children with recurrent medulloblastoma. 68 recurrences in total; 15 recurrences were asymptomatic, and 50 were identified on the basis of symptoms. Clinical data were not available in three children.](image-url)
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for at least 7.5 years, although 51 of the 53 recurrences occurred within 5.5 years. A time to recurrence of 7.5 years has previously been reported, and the longest time reported is 19 years. Limiting surveillance times to every 3 years for children older than 2 years and to every 2 years in children younger than 2 years, as suggested by Sargent, would have missed nine of 51 recurrences in older children and one of two recurrences in younger ones in our study group. It would seem unacceptable to embark on a surveillance protocol that did not continue long enough to detect almost 20% of recurrences.

Limitations of the Study

A limitation of this study is the variation in the intervals between imaging studies. This was partly overcome by considering the imaging interval for the 1st and subsequent years separately, because we require more frequent imaging sessions during the 1st follow-up year. The only way to test the value of surveillance imaging robustly would be to randomize large groups of patients prospectively to different imaging protocols. To overcome ethical problems, 6- or 8-month imaging intervals could be compared with our current 1-year imaging protocol.

A study of this size, lasting for 14 years, inevitably covers some variation in treatment protocols, although the core treatment remains the same. This study was not designed to test the effects of adjuvant therapy and was complicated by varying dose protocols, timing, and duration of treatment among patients. Following a single recurrence, however, a greater proportion of children in the surveillance imaging–detected recurrence group was treated with additional surgery and chemotherapy than in the symptomatic group. This most likely reflects the fact that the general health of children presenting with surveillance imaging–detected disease is better and they are better able to tolerate further treatment. Although treatment decisions were not made while blinded to the mode of presentation, we believe that they were made independent of the mode of presentation.

Alternatively, the surveillance imaging–detected recurrence group could represent children with tumors that behave biologically “better” than those children who present with symptomatic recurrences. Any increase in the frequency of surveillance imaging may result in the earlier asymptomatic detection of a number of “poorer” biologically active tumors, and fail to demonstrate improved survival in children who undergo increased surveillance imaging.

Rationale for Surveillance Imaging

The rationale for surveillance imaging is to identify recurrences as soon as possible so that early secondary therapies may potentially improve outcome. The data from our series indicate that the interval between surveillance images should be every 3 to 4 months for all children within the 1st year and every 6 to 8 months in subsequent years to incorporate the median time between recurrences (Table 7). We would recommend that imaging studies be obtained for a minimum period of 5 years and 6 months, and a maximum period of 7.5 years.

Although only 37% of follow-up studies included imaging of the spine, no child in our study presented with recurrent spinal leptomeningeval disease alone. In one small study, spinal tumor recurrence alone occurred only in children with metastatic disease at presentation, and the authors advocated cranial surveillance imaging in these children only until a recurrence occurred. We recommended the practicable addition of a single contrast-enhanced sagittal image of the spine to all surveillance images because it is possible, albeit rare, for recurrent spinal disease to occur alone.

For the last 3 years it has been our practice to collect lumbar CSF samples either 10 days following surgery or at the time of tumor recurrence. It has been shown that a cytological examination of lumbar CSF is better than a cytological examination of CSF from a shunt for the detection of leptomeningeval disease in a group of children with brain tumors. A 100% agreement between the findings of MR imaging and those of lumbar CSF has been reported in the detection of leptomeningeval disease in a study of a small number of children with brain tumors; however, in a larger study of children with medulloblastoma or primitive neuroectodermal tumor, cytological examination of lumbar CSF and MR imaging of the spine together improved the detection of leptomeningeval disease by 14 to 18%.

All protocols for the treatment of tumors in children should take into consideration the medical value of surveillance imaging and offset this against the following: 1) the psychological implications to both the family and child of recurrent hospital visits; 2) the medical risks of sedation and general anesthesia; and 3) the resource implications for departments of anesthesia and radiology. Nevertheless, this study shows that the overall length of survival was improved in patients in whom tumor recurrence was detected by surveillance imaging and that treatment protocols for childhood medulloblastoma should include surveillance imaging.

References

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D. E. Saunders, et al.

Manuscript received August 30, 2002. Accepted in final form April 21, 2003. Research conducted at the Great Ormond Street Hospital for Children National Health Service Trust benefits from research and development funding received from the National Health Service directorate.

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