The outcome of many childhood cancers has improved tremendously during the last four decades because of early diagnosis, improved surgical technique, and the use of cytotoxic drugs with or without radiation therapy. Among the complications of cancer therapy, hematological and vascular changes are potentially associated with ICH. Although ICH is a recognized complication of cancer and its treatment, few reports exist regarding the causes and outcome of ICH in children with cancer.

Hemorrhage within the intracranial cavity can cause severe morbidity, including death, and survivors may sustain significant neurological deficits. Few data are available regarding the incidence of ICH, related clinical phenomena, and long-term morbidity in survivors of childhood cancer. We report the occurrence of ICH in a population of children who were undergoing cancer therapy or prolonged post-treatment follow up at the time of ICH; data were analyzed with the goal of revealing potential causes and assessing clinical outcome.

Clinical Material and Methods

Patient Population

After approval from the Institutional Review Board had been obtained, patients with ICH were identified from hospital and neurology clinic databases. Inclusion criteria for this study consisted of a cancer diagnosis, treatment at our institution, and the development of ICH confirmed on imaging or surgically between January 1985 and January 2003 were retrospectively reviewed. Assessment tools included the Karnofsky Performance Scale (KPS), Glasgow Coma Scale (GCS), and the Fisher exact and Student t-tests.

Among the 51 cases, 30 involved brain tumors, 19 leukemia, and two lymphoma. The treatment group (Group 1) comprised 36 patients who suffered ICH during cancer treatment; the posttreatment group (Group 2) consisted of the 15 patients who suffered ICH after the completion of cancer treatment. The types of ICH included 22 cortical, four subcortical, 17 subdural, five brainstem, one subarachnoid, one epidural, and one ventricular. Thrombocytopenia was present in nine patients (25%) in Group 1. More patients in Group 2 (87%) than in Group 1 (44%) underwent cranial radiation treatment. Patients in Group 1 experienced a higher incidence of coagulopathy (37%) and ICH-related death (25%) than those in Group 2 (0 and 7%, respectively). Decrease in KPS and GCS scores of greater than 30 and greater than 3, respectively, at the time of ICH were indicators of increased mortality. Of the 17 children with subdural ICH, 13 suffered the hemorrhage following treatment for hydrocephalus and three patients suffered ICH associated with thrombocytopenia. In the 33 children alive at the 3-month follow-up examination after the ICH, no difference existed in the mean KPS scores pre- and post-ICH.

Conclusions. Treatment for hydrocephalus, coagulopathy, thrombocytopenia, and hemorrhage into the tumor were the most probable causes of ICH among patients in Group 1. Radiation-induced vasculopathy was a possible cause of ICH in the patients in Group 2. Significant decline in the patient’s neurological status at the time of ICH is a poor prognostic factor, but those patients who survive cancer and ICH are likely to regain neurological function.

Key Words • intracranial hemorrhage • cancer • radiation treatment • pediatric neurosurgery
2003. Patients treated prior to 1985 were excluded because modern neuroimaging was not then universally available at our institution. In general, approximately 90% of childhood cancer and ICH survivors maintain follow up at our institution until the age of 18 years and at least for 10 years post-treatment. For the purpose of our study, an ICH was defined as the presence of blood in brain parenchyma, ventricles, or between the meningeal layers. Hospital charts of the children were reviewed for demographic data; clinical presentation of ICH; cancer type, location, and treatment; coagulation status; and patient’s neurological status. The neurological status of each child before ICH, at the time of hemorrhage, and at 3 months post-ICH were assessed retrospectively by using the KPS and GCS. Thrombocytopenia was defined by a platelet count of less than 40,000/μl. Coagulopathy was defined as the presence of blood in brain parenchyma, ventricles, or between the meningeal layers. Hospital charts of the children were reviewed for demographic data; clinical presentation of ICH; cancer type, location, and treatment; coagulation status; and patient’s neurological status. The neurological status of each child before ICH, at the time of hemorrhage, and at 3 months post-ICH were assessed retrospectively by using the KPS and GCS.

Thrombocytopenia was defined by a platelet count of less than 40,000/μl and coagulopathy was defined by a greater than 100% prolongation of prothrombin time or partial thromboplastin time compared with the control.

**Types of ICH**

The cause of the death was defined as death due to disease if the child died of cancer and death due to hemorrhage if the child died as a direct result of the ICH. Therapeutic interventions for ICH were also recorded. A single investigator (R.B.K.), blinded to the clinical status of the child, reviewed neuroimaging studies of all the children. The hemorrhage location was defined as cortical if the hematoma formed superficial to the basal ganglia, with or without involvement of the cortex, and subcortical if the hemorrhage occurred at or medial to the basal ganglia. Other locations defined included cerebellar, brainstem, ventricular (within the ventricular cavities), epidural (between the cranium and dura mater), subdural (between the dura and arachnoid), and subarachnoid (between the arachnoid and pia mater). The size and location of the blood clot as well as the presence of mass effect and midline shift were noted. The volume of each parenchymal hemorrhage was calculated by multiplying maximum diameters in three different planes. The maximum width of the hematoma in the axial plane was used to measure subdural and other extraaxial hemorrhages. Because of the small number of some variables, statistical analysis was performed using the Fisher exact test and the unpaired Student t-test.

**Results**

**Patient Population and Clinical Features**

Ninety-five children who had possibly suffered an ICH were identified from the database search. After a review of charts and neuroimaging studies had been conducted, diagnoses of both cancer and ICH were confirmed in 51 of the 95 children, and these children compose the patient population in this report. Exclusion criteria included a lack of availability of charts or neuroimaging studies and the absence of a diagnosis of cancer. No patient in this study had incurred prior head trauma or a central nervous system infection at the time of the ICH. Of the 51 children with ICH, 25 suffered primary brain tumors: five from brain metastases due to solid primary tumor outside the central nervous system, 18 from acute leukemia, two from non-Hodgkin lymphoma, and one from chronic myeloid leukemia. With the exception of two patients with pineal tumors who underwent stereotactic biopsy, all patients suffering from primary brain tumors underwent attempted gross-total resection. No patient harboring a metastatic brain tumor had undergone a neurosurgical procedure prior to the ICH.

Patients were divided into two groups: Group 1 comprised those 36 patients who suffered ICH after cancer diagnosis or during antineoplastic therapy and Group 2, those 15 patients who suffered ICH at least 1 month after the completion of therapy. The study population included 28 boys and 23 girls (Table 1). The median age of the 51 children at the time of ICH was 10 years (95% CI 9–13 years); 9 years (95% CI 7–12 years) in Group 1 and 14 years (95% CI 10–17 years) in Group 2. Overall median age at the time of cancer diagnosis was 7 years (95% CI 6–10 years); 9 years (95% CI 6–10 years) in Group 1 and 4 years (95% CI 3–10 years) in Group 2. The median duration of the follow-up period after ICH was 8.8 months: 4 months (95% CI 11–38 months) in Group 1 and 49 months (95% CI 29–100 months) in Group 2. A higher mortality rate among the patients in Group 1 within 90 days of ICH (42% in Group 1 compared with 20% in Group 2) and a lower percentage of patients in Group 1 alive at the study’s conclusion (36% in Group 1 compared with 67% in Group 2) partly account for the difference in follow-up duration between the two groups.

Eleven children in Group 1 were receiving chemotherapy at the time of ICH. Twenty-one children in the study underwent whole-brain radiation treatment up to a median dosage of 30 Gy (95% CI 22–34 Gy), and 21 children underwent focal radiation treatment (median dosage 54 Gy; 95% CI 41–56 Gy). In total, 29 children underwent radiation treatment; some children underwent whole-brain and focal radiotherapy. Of the 36 children in Group 1, 16 (44%) underwent radiation treatment to the brain, including five who underwent radiotherapy after the ICH; 13 (87%) of the 15 children in Group 2 underwent radiation to the brain. Median age at radiation treatment was 5 years (95% CI 5–10 years) for the 29 children who underwent radiotherapy: 5 years (95% CI 4–11 years) in Group 1 and 7 years (95% CI 5–11 years) in Group 2. Median time from...
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The radiation treatment to ICH for the children in Group 2 who underwent radiotherapy was 74 months (95% CI 39–134 months) and 3 months (95% CI 0.1–13 months) for the children in Group 1 who underwent radiation treatment before the ICH. The proportion of children who underwent radiation treatment was significantly larger in Group 2 compared with Group 1 (p = 0.0001).

Thrombocytopenia was present at the time of hemorrhage in nine children (25%) in Group 1 and none in Group 2 whereas coagulopathy was present in nine (37%) of the 24 patients tested in Group 1 and none of the eight tested in Group 2. Nineteen patients underwent VP shunt placement—15 in Group 1 and four in Group 2.

Types of ICH and Tumor

The types of ICH included 22 cortical (16 in Group 1, six in Group 2), four subcortical (three in Group 1, one in Group 2), 17 subdural (12 in Group 1, five in Group 2), five brainstem (three in Group 1, two in Group 2), one ventricular (Group 1), one subarachnoid (Group 2), and one epidural (Group 1) (Table 2). Of the 29 patients with brain tumors, 10 (five with primary brain tumor, five with metastatic tumor) suffered hemorrhages into the tumor, 13 suffered subdural ICH, three experienced multiple small cortical hemorrhages, two had brainstem hemorrhages, and one a subarachnoid hemorrhage; one experienced thrombocytopenia and two of the eight tested experienced coagulopathy. Of the 10 children who suffered hemorrhages into the tumor, five died of the hemorrhage (50% mortality rate). Three children with acute leukemia suffered asparaginase-related dural venous sinus thrombosis and cortical hemorrhage. Eighteen children died within 3 months of ICH; 10 deaths were attributed directly to the ICH, and all but one of the ICH-related deaths occurred in Group 1 (p = 0.005).

Of the 17 children with subdural ICH, 13 harbored primary brain tumors (five medulloblastoma, four low-grade glioma, and one each primitive neuroectodermal tumor, ependymoma, pineal tumor, and atypical teratoid tumor). Children without brain tumors who experienced subdural ICH included four patients with acute leukemia (two lymphoblastic and two myeloid). Three children with acute leukemia experienced thrombocytopenia, one of whom also suffered from coagulopathy, and the fourth suffered a subdural ICH after a brain biopsy. Among the 17 children with subdural ICH, 11 patients suffered hemorrhages subacutely after undergoing placement of a VP shunt for increased intracranial pressure and hydrocephalus, and two suffered hemorrhages after posterior fossa tumor resections for the treatment of hydrocephalus. Only one of the 13 patients with hydrocephalus-related ICH suffered from thrombocytopenia at the time of identification of the subdural ICH. In two of these 13, platelet counts were less than 100,000/µL and of the six tested, none demonstrated evidence of coagulopathy. One patient with acute myeloid leukemia died of subdural ICH.

Five children in Group 2 suffered recurrent small parenchymal hemorrhages, mostly at the gray–white matter junction and in deep white matter (Fig. 1). None of these five suffered thrombocytopenia or coagulopathy, but all had previously undergone radiation treatment (focal in two patients and whole brain in four). Hemorrhagic cavernoma-

![Fig. 1. Magnetic resonance images obtained in a child who suffered recurrent ICH. Axial T1-weighted (A) and proton-density weighted (B) images demonstrating little evidence of acute or old hemorrhages. Multiple hemosiderin deposits from old hemorrhages are visible in the deep white matter and the gray–white matter junction on the gradient-echo image obtained in the same child (C).](image-url)
like lesions existed within the field of radiation treatment in one patient who underwent focal radiation treatment only.

**Performance Status**

Twenty-two children demonstrated no change in their KPS score at the time of ICH diagnosis; of these 22, eight suffered cortical ICH (five in Group 1, three in Group 2), one ventricular (Group 1), and 13 subdural (nine in Group 1, four in Group 2). Median KPS scores revealed significant neurological decline at the time of ICH, including the scores for those patients who survived at least 3 months post-ICH \( (p < 0.0001 \) and \( p = 0.01 \), Table 3). For those alive 3 months after the ICH, however, there was no difference in the KPS scores before and 3 months post-ICH \( (p = 0.6) \). Mean KPS scores decreased by 51 points (95% CI 35–67 points) at the time of ICH in the children who died of hemorrhage compared with a decrease of 13 (95% CI 7–19 points) in the 41 other children; this difference was significant \( (p < 0.0001) \). A decrease of 30 points or greater in KPS scores occurred at the time of ICH in 90% of the 10 children who died of ICH and in 17% of the other 41 patients \( (p < 0.0001) \). A decrease in GCS scores of greater than three points occurred at the time of ICH in 12 patients (11 in Group 1, one in Group 2); nine of these patients suffered cortical hemorrhages and one patient each ventricular, epidural, and subdural ICH. Of the 10 children who died of ICH, eight demonstrated a greater than three-point decrease in GCS scores at the time of ICH compared with four of the remaining 41 children \( (p < 0.0001) \). Three children with independent functional status prior to the ICH demonstrated dependency for activities of daily living 3 months after ICH.

**Imaging Results**

In 18 children midline shifts of the paramedian structures (\(< 1 \text{ cm in 15, } > 1 \text{ cm in three}\) were revealed on neuroimaging, but these lesions did not predict ICH-related death. Two of the three patients with midline shifts greater than 1 cm died of ICH; however, small numbers preclude statistical analysis. Median volume of hematoma in the 23 patients with supratentorial (cortical and subcortical) parenchymal ICH in whom neuroimaging was performed measured 63 ml (range 1–640 ml, 95% CI 60–234 ml). There was no difference in the mean ICH volume in the seven children who died of supratentorial parenchymal ICH compared with that in those who did not die of this condition (156 ml compared with 129 ml, \( p = 0.3 \)).

Median width of the subdural ICH was 1 cm (range 0.5–6.5 cm); seven patients with subdural ICH demonstrated evidence of midline shift.

**Surgical Procedures**

Hydrocephalus-related subdural ICHs appeared mostly hypodense on computerized tomography scanning. Nine patients with subdural ICH were treated surgically: three underwent placement of a subdural shunt, four underwent craniotomy, and two, burr hole evacuation. Five of these nine surgically treated patients experienced complete resolution of subdural fluid collection and in four the fluid collection in the subdural space persisted. Of the 10 children with subdural ICH who were alive at the end of this study, seven experienced no subdural collection and three maintained stable asymptomatic subdural collection. Six children underwent craniotomy for hematoma evacuation (four cortical, two subcortical); two died of hemorrhage, and four were alive at the last follow-up examination. In the four patients who survived, KPS and GCS scores decreased by 70 and eight points, 60 and 12, 20 and one, and 10 and one points, respectively. At the last follow-up examination the four surviving patients demonstrated KPS scores of 90, 100, 40 and 100; the two children with the greatest decline in KPS scores recovered sufficiently to achieve scores of 90 and 100. A child with a cerebellar ICH died of the hemorrhage despite having undergone craniotomy and clot evacuation. Stereotactic biopsy was performed in a child with brainstem hematoma and in another child with a cortical hematoma.

**Discussion**

As we suspected, ICH is an uncommon event in children with cancer; indeed, we could document only 51 such cases. During the study period at our institution, 30 (3%) of 1036 children with brain tumors and 18 (1%) of 1597 with acute leukemia suffered an ICH. Given that this is a retrospective study, however, our findings may underestimate the incidence of ICH in children with cancer. In patients with brain tumor and acute leukemia, ICH has been reported in small patient series.\(^{7,12}\) In our study, cortical hemorrhage was the most common type followed by subdural. Conditions coincident with cortical hemorrhage included blood clotting disorders (thrombocytopenia or prolonged prothrombin time or partial thromboplastin time) and hemorrhage into a brain tumor; clotting disorders were mostly

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**TABLE 3**

Karnofsky Performance Scale scores for children with cancer before, at the time of, and 3 months post-ICH*  

<table>
<thead>
<tr>
<th>KPS Score</th>
<th>No. of Patients</th>
<th>Median Score (95% CI)</th>
<th>Mean Change in Score (p value)</th>
<th>At ICH</th>
<th>3 mos Post-ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ICH</td>
<td>At ICH</td>
<td>Post-ICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>51</td>
<td>80 (70–80)</td>
<td>60 (50–60)</td>
<td>NA</td>
<td>−20 (&lt;0.0001)</td>
</tr>
<tr>
<td>alive</td>
<td>33</td>
<td>80 (72–83)</td>
<td>70 (58–73)</td>
<td>NA</td>
<td>−12 (0.01)</td>
</tr>
<tr>
<td>dead</td>
<td>18</td>
<td>80 (61–84)</td>
<td>30 (26–50)</td>
<td>NA</td>
<td>−35 (0.0001)</td>
</tr>
<tr>
<td>died of ICH</td>
<td>10</td>
<td>90 (61–93)</td>
<td>30 (18–34)</td>
<td>NA</td>
<td>−51 (&lt;0.0001)</td>
</tr>
<tr>
<td>died of other</td>
<td>41</td>
<td>80 (69–81)</td>
<td>70 (54–70)</td>
<td>NA</td>
<td>−13 (0.01)</td>
</tr>
</tbody>
</table>

* NA = not available.
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present in hematological malignancies. Subdural bleeding, however, occurred predominantly in patients with brain tumors who were undergoing treatment for hydrocephalus, such as VP shunt placement or resection of a posterior fossa tumor. The second most common cause of a subdural ICH was thrombocytopenia. Subdural hematoma can develop after VP shunt placement and may result from tearing of the bridging subdural veins, which is caused by the traction of collapsing ventricles or the development of a pressure difference between the ventricular and subarachnoid spaces. At our institution, we surgically treat shunt-induced subdural ICH if it is symptomatic, if the ICH increases in size, or if it demonstrates a persistently higher density than cerebrospinal fluid on neuroimaging studies; the latter, in our opinion, increases the risk of chronic subdural collection, calcification, and neurological morbidity. 

Thrombocytopenia and coagulopathy contributed to the development of ICH in a significant proportion of children in Group 1. The blood vessels of brain tumors are immature and this factor may have contributed to hemorrhaging into the brain tumor, which was another common event in Group 1 (25%) and an event with a high mortality rate (50%). A short interval between radiation treatment and ICH in Group 1 probably indicates the absence of a causal relationship between radiation treatment and ICH. Radiation-induced vasculopathy, however, was perhaps a cause of delayed ICH in patients in Group 2. A median duration of 79 months (95% CI 33–125 months) in Group 2 between radiation treatment and ICH may be evidence of an increasing risk of ICH with the passage of time. Five children in Group 2 suffered multiple, recurrent small hemorrhages at the gray–white matter junction or in the deep white matter, which are the watershed areas of the penetrating blood vessels. Delayed hemorrhage and the development of telangiectasia and cavernoma-type brain lesions following radiation treatment have been reported before and may be related to radiation-induced small vessel disease. Significant acute morbidity and a mean decrease in KPS scores of 20 points (95% CI 13–27 points) occurred at the time of ICH. Ten children (20%) died as a direct result of hemorrhage; nine were in Group 1. Decreases in the KPS score of greater than 30 points and the GCS score of greater than 30 points at the time of ICH were associated with increased mortality; a decrease in the GCS score at the time of ICH is a known factor of poor prognosis. Children who survived the ICH and tumor for 3 months, however, demonstrated excellent neurological outcome and no significant change in their mean KPS scores before and at 3 months after the ICH; only three of the 33 survivors became dependent with respect to activities of daily living after having been independent prior to the ICH.

Conclusions

Parenchymal supratentorial and subdural hemorrhages are the two most common types of ICH in cancer patients. Treatment regimens for hydrocephalus, thrombocytopenia, coagulation abnormalities, and hemorrhage into the tumor were possible causes of ICH in patients in Group 1, whereas radiation-induced vasculopathy probably contributed to the posttreatment ICH in those in Group 2. Hemorrhage from radiation-induced vasculopathy may occur many years after radiotherapy and the risk may increase with time. Significant decline in neurological status at the time of ICH is a poor prognostic factor, but children who survive the hemorrhage and the cancer are likely to regain functional independence.

References


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