In the treatment of brain tumors in pediatric patients, difficulties arise during attempts to differentiate recurrent tumor from the effects resulting from treatment. Treatment effects can arise from radiation treatment and/or chemotherapy, and the effects of the former usually occur in the following three distinct time periods: 1) acute reactions (during or immediately after therapy); 2) early-delayed reactions (between 3 to 6 weeks and 3 to 6 months after therapy); and c) late-delayed reactions (beginning between 6 and 12 months until years after therapy). Acute and early-delayed reactions are often transient and self-limiting, whereas late-delayed reactions may progress to necrosis, ischemia, and infarction. In contrast, we describe enhancing asymptomatic TBLs that occurred outside of the tumor bed of brain neoplasms in pediatric patients during the late-delayed period of treatment; these lesions were clinically occult and completely resolved without neuroimaging or neurological sequelae.

Clinical Material and Methods

Patient Population

Of the pediatric patients with brain tumors who were treated at our institution between May 1990 and August 2001, those who were identified from the neuroimaging database as having undergone 3D radiation dosimetry and who possibly harbored TBLs were included in this study. We identified a total of 25 pediatric patients with brain tumors and possible transient lesions detected on MR images. Of these 25 patients, 14 were excluded because their MR imaging findings were more consistent with tumor progression or metastatic disease (five patients), radiation necrosis...
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was undertaken.

of dosimetry, chemotherapy protocols, and medical records identified as having harbored TBLs, a review of radiation treatment. Annual studies were advised thereafter. Patients were usually examined every 6 months for another year and then one to two times per year until 5 years after initial treatment. Annual studies were advised thereafter. Patients underwent additional MR imaging examinations if necessary.

Magnetic resonance images of the brain were obtained using 1.5-tesla magnets and the following sequences: sagittal T1-weighted, GE (TR 165 msec, TE 4.7 msec, number of excitations 2 with FA 60°) axial spin echo proton density and T2-weighted images (TR 3500 msec, TE 17–105 msec, number of excitations 1); unenhanced axial T1-weighted GE images (TR 165 msec, TE 4.7 msec, number of excitations 2, FA 60°); followed by axial and coronal T1-weighted contrast-enhanced gadodiamide (Omniscan; Amersham Health, Inc., Nycemed, Norway), with thin 3D magnetization-prepared rapid acquisition TR 15 msec, TE 5 msec, FA 15° contrast-enhanced images, with 2-mm contiguous sagittal and coronal reconstruction through the tumor bed. Preoperative neuroimaging was usually performed at outside institutions, but follow-up surveillance images were nearly always obtained at our institution.

Radiation Dosimetry

The radiation dose at the site of a TBL was determined by coregistering the MR image on which the abnormality was demonstrated to the 3D treatment dosimetry that was available for each patient. The lesion was contoured using radiation treatment-planning software, and from the dosimetry of the lesion an average dose was determined. The time of the onset and time to resolution of the TBL after completion of radiation therapy was also recorded.

Chemotherapy Protocols

All protocols were reviewed, and the total doses of individual chemotherapeutic agents along with the timing of chemotherapy in relationship to the onset and resolution of the TBL were recorded.

Chart Review

All medical records were reviewed, and neurological examinations performed during the course of treatment were evaluated. Any neurological signs or symptoms occurring during the time period of the TBL were recorded.

Results

Four of the tumors were supratentorial (OPG, pineoblastoma, PNET, and GBM), and seven were infratentorial (six medulloblastoma, and one ependymoma). Five patients had undergone gross-total resection, four subtotal resections, one biopsy only, and one patient suffering from OPG underwent neither biopsy nor surgery. Following surgery, patients were treated on a range of pediatric protocols for brain tumors; 10 received combination chemotherapy for brain tumors; 10 received combination chemotherapy in relationship to the onset and resolution of the TBL were recorded.

Magnetic Resonance Imaging Examinations

Neuroimaging studies were prospectively reviewed by a neuroradiologist (J.W.L.) and retrospectively by a second neuroradiologist (K.J.H.). Data gathered from the MR images included the following: 1) size, location and signal characteristics of the TBL; 2) time of onset, and time to resolution of the TBL; 3) proximity of the TBL to the primary tumor; 4) presence of residual tumor, recurrent tumor, or metastatic disease at the time of follow-up MR imaging examination; and 5) development of focal radiation necrosis, ischemia, or infarction. Protocols routinely included MR imaging examinations in the immediate postoperative period and at 3-month intervals following treatment for a duration of 12 to 18 months. Patients were usually examined every 6 months for another year and then one to two times per year until 5 years after initial treatment. Annual studies were advised thereafter. Patients underwent additional MR imaging examinations if necessary.

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Treatment effects in children with brain tumors

<table>
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<tr>
<th>Case No.†</th>
<th>Original Tumor Location</th>
<th>TBL Location (No.)</th>
<th>RT Dose at TBL</th>
<th>Size of Largest Enhancement Foci (mm)</th>
<th>Associated T2-weighted Hyperintensity</th>
<th>Time From Start of RT to TBL (mos)</th>
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*Mid = middle; NA = not applicable; ptwcm = periventricular white matter; RT = radiation therapy; temp = temporal; vermis = vermis cerebelli.
†Patients in Cases 1, 3, and 11 had TBLs in more than one location.

Summary of MR imaging findings and TBL characteristics

Images. The enhancement borders of the lesions were distinct in 10 cases and ill-defined in seven. The corresponding hyperintense T2-weighted signal abnormalities were larger than the region of enhancement in two cases (Fig. 1), the same size in 12 cases, and smaller in three cases. No mass effect was present. Transient brain lesions occurred in the brainstem (six lesions), cerebellum (five lesions), middle cerebellar peduncle (two lesions), cerebral hemisphere (three lesions), and periventricular white matter (one lesion). Fourteen lesions occurred in the deep white matter and three in the gray-white matter junction. One patient harbored more than six lesions (Case 7; Fig. 2), nine patients two to five lesions each, and seven patients one lesion each at each location. The lesions ranged in size from 4 to 10 mm. The TBLs occurred at a median of 10 months (mean 14.8 months, range 3–97 months) after the beginning of chemotherapy and a median of 11 months (mean 10 months, range 4–21 months) after the beginning of chemotherapy. Of note, one patient who did not undergo chemotherapy harbored a TBL that occurred much later (97 months from the beginning of radiation therapy) than the occurrence of TBLs in 10 patients who received both chemotherapy and radiation therapy. All of the lesions occurred in the highest-dose radiation field (median dose 55.8 Gy, minimum dose 51 Gy). The lesions resolved completely as documented by neuroimaging evidence—abnormal T2-weighted hyperintensity and enhancement—during a median period of 3 months (mean 5.5 months, range 2–12 months) from the first observation. Patients were followed for a median of 14 months (mean 16.4 months, range 2–40 months) after the resolution of the TBLs.

During the extended follow-up period, additional complications of therapy occurred in the high-dose radiation field in locations distinct from that of the resolved TBL; these complications included focal radiation necrosis (three patients), multiple lacunar infarcts (two patients), and posterior inferior cerebellar artery ischemic infarct (one patient). There was one hemorrhagic infarct (one patient), near an area in which a TBL had resolved 12 months earlier. Interestingly, one patient suffered from three of these complications: lacunar infarct, posterior inferior cerebellar artery ischemic infarct, and hemorrhagic infarct. Radiation necrosis was verified by MR spectroscopy in two cases, and residual tumor/radiation necrosis was confirmed surgically in another case. In no patient was a biopsy performed at a site of TBL. Currently six patients remain stable with no evidence of disease. In three patients stable residual disease is present but there is no progression. One patient died of progressive disease and another died of metastatic leptomeningeal disease.

Interpretation of Radiation Dosimetry and Dose-Volume Data

All of the patients included in this study were treated with conformal radiation therapy alone or in combination with craniospinal radiation therapy.111 These techniques rely on 3D imaging to define and target the tumor and to distinguish it from normal tissue, which in turn makes it possible to estimate the dose accurately for any tissue struc-
t cure. The neuroimaging study demonstrating the TBL was registered to the 3D dosimetry that was available for each patient. It was determined that TBLs were limited to tissue structures that received a median dose of 55.8 Gy (range 51–66 Gy), which was within the range of the prescribed dose for the treated volume (Fig. 3).

Interpretation of Chemotherapy Data

All of the six patients with medulloblastoma received four cycles of postradiotherapy high-dose myeloablative therapy that consisted of CDDP/CTX/VCR followed by stem cell rescue. Three of these patients were classified as high-risk and received topotecan before radiation treatment. The patient with the ependymoma and the patient with the pineoblastoma, the only patient younger than the age of 2 years, also received thiotepa. The one patient with the pineoblastoma, the only patient younger than the age of 2 years, also received thiotepa. The one patient with the pineoblastoma was treated with procarbazine, lomustine, and carboplatin after radiation treatment, and the patient with OPG was treated with carboplatin/VCR prior to radiation treatment. All patients were treated on therapeutic protocols and the median cumulative doses for topotecan, etoposide, procarbazine, lomustine, and carboplatin were within the normal range for conventional therapy. Median doses for VCR, CDDP, CTX, and thiotaepa were acceptable for high-dose strategies. No experimental or biological agents were used.

The chemotherapeutic dose levels used for patients with TBLs were not appreciably higher than chemotherapeutic doses used at our institution for other patients with brain tumors. In fact, dose levels used in the patients reported here were comparable to those used for the majority of other patients with brain tumors, who are typically treated with aggressive chemotherapeutic regimens at our institution. From this finding one might infer that the difference between patients who develop TBLs and patients who do not develop TBLs may in part pertain to the patient's genotype rather than the chemotherapeutic dose level.

Discussion

Although the development of novel therapies for the treatment of central nervous system tumors has dramatically affected survival statistics over the past several decades, a critical analysis of treatment toxicities is complicated by the complexity of radiotherapy and multiagent chemotherapeutic treatments. We have described 11 patients treated on multiple protocols with 17 separate foci of radiation necrosis. The finding that TBLs were limited to the high-dose treatment volume indicates that they are primarily an effect of the radiotherapy treatment. The finding that TBLs were limited to the high-dose treatment volume indicates that they are primarily an effect of the radiotherapy treatment.

Distinguishing TBL from radiation necrosis is critical because TBLs may develop after radiotherapy and chemotherapy regimens. Therefore, it is important to identify radiographic features that allow one to distinguish TBLs from radiation necrosis or mass effect. Follow-up T1-weighted images demonstrated resolution of enhancement pattern, signal characteristics on all pulse sequences, and the delay in contrast enhancement between patients who develop TBLs and patients who do not develop TBLs may in part pertain to the patient's genotype rather than the chemotherapeutic dose level.

The median age of the patients at the time of diagnosis was 6.1 years, range 0.8–16 years. Six patients were male and four female. Four of the patients were older than the age of 2 years, 10 of whom registered to the 3D dosimetry that was available for each patient. It was determined that TBLs were limited to tissue structures that received a median dose of 55.8 Gy (range 51–66 Gy), which was within the range of the prescribed dose for the treated volume (Fig. 3).

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Treatment effects in children with brain tumors

at 2 years from initiation of therapy).\textsuperscript{4} In our study, lesions were determined dosimetrically to fall within the prescribed high-dose region for the given patient in 11 children, 10 of whom also underwent a variety of chemotherapeutic regimens. We distinguish the imaging, temporal, spatial, and neurological characteristics of these transient lesions and describe how they differ from acute and early-delayed treatment injury, and from recurrent tumor and radiation necrosis.

Transient enhancing foci with or without associated neurological symptoms have been well described during the first 3 months following radiation treatment.\textsuperscript{1–3,5,6} The TBLs we describe, however, occurred predominantly during the late-delayed time period of treatment, a median of 10 months after the beginning of radiation therapy (median 9 months, range 3–24 months if the outlying patient who did not receive chemotherapy is excluded), and 11 months after the beginning of chemotherapy. Registration of the imaging study that demonstrated the TBLs to the 3D radiation dosimetric map confirmed that all lesions occurred within the high-dose volume (minimum observed dose 51 Gy). That TBLs were limited to the high-dose treatment volume indicates that they are primarily an effect of radiation therapy. The finding that the onset of TBLs was markedly delayed in the patient who was treated with radiation alone, however, provides evidence that chemotherapy can potentiate the radiation effect.

Distinguishing a TBL from a recurrent tumor was made possible by careful comparison of the original tumor enhancement pattern, signal characteristics on all pulse sequences, and the location of the original tumor compared with that of the TBL. By definition, all TBLs occurred outside the tumor bed. Because of the obvious parenchymal involvement in patients whose tumors commonly had leptomeningeal metastasis (six medulloblastoma, one PNET, one pineoblastoma), most of these lesions were initially deemed to be the result of possible treatment effects and were observed with short-interval follow up. All lesions were small (≤ 1 cm), hyperintense, predominantly white matter–enhancing foci, with either distinct (10 lesions) or ill-defined (seven lesions) patterns of enhancement. It is probable that our protocol-driven imaging, which was quite frequent, allowed for more sensitivity in detecting the TBLs. Additionally, because the severity of MR imaging–documented changes correlated with the severity of clinical symptoms, it is not surprising that the small lesions we describe were asymptomatic.\textsuperscript{4,5,7,10} Further, based on the neuroimaging characteristics of the lesions, we were confident that the lesions were not recurrent tumors and, therefore, did not recommend biopsy.

In future studies, it may be appropriate to study TBLs by using diffusion tensor imaging to identify reduced fractional anisotropy, which has been associated with demyelination,\textsuperscript{9} or T1\textsuperscript{3}–weighted GE MR imaging to look for tiny hemosiderin deposits.\textsuperscript{11} We think that MR spectroscopy is unlikely to provide much insight into TBLs because the smallest voxel currently identifiable by MR spectroscopy (~1 cm\textsuperscript{3}) is probably too large to include the lesion without also including a substantial amount of normal brain surrounding the lesion. Such partial-volume inclusion of normal tissue would substantially reduce the sensitivity of MR spectroscopy to any metabolite abnormality within the TBL itself. Analysis of smaller voxel size, however, is likely to become possible in the future with more widespread use of higher field strength magnets.\textsuperscript{5}

Radiation-induced brain injury has been classified into acute reactions, early-delayed reactions, and late-delayed reactions. Acute reactions occur during or within the first
6 weeks, and early delayed reactions between 3 weeks and 3 months after completion of radiation therapy. Because most patients are asymptomatic during the acute- and early-delayed time period, or suffer from transient, self-limiting symptoms with a benign outcome, histological correlation is rarely required.1 In contrast, late-delayed reactions occur several months to many years after radiation therapy, most commonly in patients in whom doses of 50 Gy or more have been administered, and these reactions can include clinically devastating neurological effects.19

Neuroimaging findings during the acute stage may include temporary vasogenic edema with hyperintensity on T2-weighted MR images. Enhancement is uncommon and secondary to acute vasodilation and increased capillary permeability. Associated transient neurocognitive decline may also occur. Early-delayed neuroimaging findings include focal or diffuse transient demyelination, which may be associated with focal enhancement. Neurological findings may be focal and may resolve when the neuroimaging-detected abnormalities improve.18 Late-delayed complications are nearly always irreversible and can include diffuse white matter injury, radiation necrosis, mineralizing microangiopathy, cerebral atrophy, cerebral infarction, and vasculopathy.18,19 By contrast, we present a series of pediatric patients with brain tumors and transient, asymptomatic late-delayed reactions.

Prospectively distinguishing treatment effect from recurrent tumor can be extremely difficult. Kumar, et al.,12 described the neuroimaging features of pathologically proven radiation necrosis in a cohort of 148 adult patients with malignant glioma who after resection underwent treatment that included accelerated radiation treatment and multigent chemotherapy. The neuroimaging features of radiation necrosis included enhancing foci that developed within or circumscripting a nonenhancing tumor, enhancing foci that were detected at a distance from the primary tumor, in a periventricular location, or new enhancing lesions on which a soap bubble or Swiss cheese pattern was observed. Kumar and colleagues found that all focal radiation necrosis occurred within the radiation portal and concluded that T1-weighted MR imaging was not helpful in differentiating recurrent tumor from radiation necrosis. Although the TBLs we observed in the present study were within the radiation portal, they were distinguishable from recurrent tumor because of discordance with the original tumor characteristics. Furthermore, in distinction to radiation necrosis, the enhancing component of each TBL was small (<1 cm in maximal axial diameter), and the majority of TBLs were evidenced by T1-weighted MR imaging–hyperintensity less than or equal to the region of enhancement. For no lesion was mass effect, central necrosis, or the classic soap bubble or Swiss cheese enhancement pattern demonstrated (Table 2).

Our findings support the claim that treatment-related neurotoxicity might be best represented by a continuum, with mild, reversible injury (such as we observed) on one end of the spectrum and permanent radiation necrosis on the other.2 Kumar and colleagues also included in their study patients with treatment-induced white matter (52) or ven radiation necrosis in a cohort of 148 adult patients with malignant glioma who after resection underwent treatment that included accelerated radiation treatment and multigent chemotherapy. The neuroimaging features of radiation necrosis included enhancing foci that developed within or circumscripting a nonenhancing tumor, enhancing foci that were detected at a distance from the primary tumor, in a periventricular location, or new enhancing lesions on which a soap bubble or Swiss cheese pattern was observed. Kumar and colleagues found that all focal radiation necrosis occurred within the radiation portal and concluded that T1-weighted MR imaging was not helpful in differentiating recurrent tumor from radiation necrosis. Although the TBLs we observed in the present study were within the radiation portal, they were distinguishable from recurrent tumor because of discordance with the original tumor characteristics. Furthermore, in distinction to radiation necrosis, the enhancing component of each TBL was small (<1 cm in maximal axial diameter), and the majority of TBLs were evidenced by T1-weighted MR imaging–hyperintensity less than or equal to the region of enhancement. For no lesion was mass effect, central necrosis, or the classic soap bubble or Swiss cheese enhancement pattern demonstrated (Table 2).

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![Image](image.png)
Treatment effects in children with brain tumors

cortical (nine) foci of enhancement, both of which have been thought to represent milder forms of brain injury.2,12 The temporal relationship of these brain lesions to the completion of chemotherapy and/or radiation therapy, to the occurrence of radiation necrosis, or to the period of time to resolution was not reported; moreover, biopsies were not performed for these patients. In our study, the majority of the TBLs occurred in the deep white matter (14), and three occurred at the gray–white matter junction. It has been demonstrated that white matter is more sensitive to radiation injury than gray matter.2,12,13 In addition, vascular research has shown that the deep white matter has a greater number of end arteries and fewer collaterals, whereas tissue at the gray–white matter junction is characterized by a better vascular supply and therefore should be more resistant to radiation-induced vascular injury.

End-stage treatment injury, also known as radiation necrosis, in patients undergoing therapy for brain tumors has been well described. These lesions are the result of a combination of vascular injury and direct injury to the cerebral parenchyma.2 Histopathologically, there is breakdown of the capillary endothelial lining, vasodilatation, vascular ectasia, and eventual hyalinization of the capillary walls with narrowed lumen.2,7 These vascular changes, sometimes in concert with associated altered fibrinolytic activity,20 can give rise to spontaneous thrombosis and infarctions. The result is a perivascular coagulative necrosis, typically involving white matter.2 Direct injury to oligodendrocytes, axonal fibers, and microglia may also be present.2

A better understanding of the neuroimaging-documented sequelae associated with radiation therapy in combination with multiagent therapy and with radiation therapy administered alone is needed. Chemotherapeutic neurotoxicities are both dose and duration dependent. Neurotoxicities have been well documented for vinca alkaloids, alkylating agents, platinum analogs, and topoisomerase inhibitors.3 Moreover, the use of platinum analogs with radiation therapy is known to potentiate the effect of radiation.25 In our patient cohort, however, the median cumulative doses were within normal ranges or were acceptable for high-dose ranges, and all patients were asymptomatic (Table 3). The combined effects of multiagent chemotherapy and radiation therapy in this variable cohort of patients is unknown.

Although the precise pathological mechanism of TBLs remains unknown, the lesions may represent small regions of transient blood–brain barrier breakdown probably occurred at doses greater than 50 Gy.20 Cerebral atrophy predominantly involving white matter has been well described in patients undergoing radiation therapy,5,11,12,14 and small foci of volume loss could be both clinically occult and undetectable on neuroimaging studies (Fig. 1). While the TBLs we describe were transient and asymptomatic, in five of 11 patients extended follow up revealed the development of additional permanent complications that resulted from treatment. These lesions occurred in locations separate from the resolved TBLs, but all such complications were nonetheless within the high-dose radiation field. These lesions included radiation necrosis (three patients), multiple lacunar infarcts (two patients), and posterior inferior cerebellar artery ischemic infarct (one patient). In contrast to recurrent tumor or the previously described permanent late-delayed findings in treatment-associated brain injury in adult patients, the neuroimaging-detected lesions we observed, which occurred with multiple protocols, probably represent a benign form of treatment-induced brain injury in children. Patients who develop possible TBLs during the late-delayed time period should be treated with short-interval follow up. When recognized by their characteristic imaging features, location, and temporal course, TBLs are distinguishable from recurrent tumor or radiation necrosis and do not require biopsy. Further studies are needed to determine whether patients with TBLs are at an increased risk for developing more severe treatment-related brain injuries in the future.

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