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AJNR Am J Neuroradiol 1990, 11 (2) 319-324
http://www.ajnr.org/content/11/2/319

Neuroimaging of Disseminated Germ Cell Neoplasms

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The purpose of this study was to determine the role of neuroimaging in the management of patients with metastatic germ cell tumors. Retrospective evaluation of 299 patients treated in 1986 and 1987 for initial presentation or recurrence of testicular, retroperitoneal, and mediastinal germ cell tumors was performed to determine indications for neuroimaging, frequency and site of CNS metastases, and occurrence of other CNS abnormalities. Sixty-six patients required CNS imaging with myelography, CT, or MR. Studies were normal in 24 patients. Twenty patients had CNS metastases including 11 with intracranial metastases, eight with spine lesions, and one with both brain and spine involvement. Sixteen had cerebral or cerebellar atrophy of unclear origin and functional significance. Two patients had ventriculomegaly without symptoms of hydrocephalus. Four patients had questionable lesions that were never confirmed. None of the 25 asymptomatic patients with elevated serum tumor markers had brain metastases. Fifteen of 17 patients with focal neurologic deficits and three of six patients with seizures had CNS metastases.

CNS imaging to detect germ cell tumor metastases is most useful in the presence of neurologic deficits or seizures but is not useful in patients with unexplained elevation of serum tumor markers in the absence of neurologic deficits.

***AJNR* 11:319–324, March/April 1990; *AJR* 154: June 1990**

CNS involvement by disseminated germ cell neoplasms causes significant morbidity and mortality [1]. The most common of these tumors, testicular neoplasm, most frequently metastasizes to retroperitoneal and mediastinal lymph nodes, lung, and liver. CNS involvement is not uncommon; the reported prevalence was 30% in one autopsy series [2] and 15% in two large clinical reviews [3, 4]. The identification of CNS metastases is important in these patients since the therapeutic regimen will be altered by their presence. The purpose of this study was to evaluate the role of neuroimaging in the management of patients with disseminated germ cell neoplasms. The indications for neuroimaging, the frequency and site of CNS metastases, and the occurrence of other CNS abnormalities were examined.

Materials and Methods

We retrospectively evaluated 299 patients treated at our medical center for newly diagnosed or recurrent testicular, mediastinal, and retroperitoneal germ cell neoplasms from January 1, 1986, through December 31, 1987. The radiology records of these patients were reviewed to identify patients who had had neuroimaging. A complete medical chart review was then performed of 66 patients who had undergone neuroimaging with CT, MR, or myelography. The clinical indication for neuroimaging, clinical stage of disease, histologic cell type, and therapy before and after neuroradiologic evaluation were obtained from the medical records.

The patient population undergoing neuroimaging consisted of 66 males 15–51 years old (mean age, 28 years). Sites of origin included 51 testicular, nine primary mediastinal, and six primary retroperitoneal germ cell tumors. A total of 123 neuroradiologic studies were per-

Received June 20, 1989; revision requested August 8, 1989; revision received August 21, 1989; accepted August 29, 1989.

Presented at the annual meetir g of the American Society of Neuroradiology, Orlando, FL, March 1989.

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0195-6108/90/1102-0319

formed in the patient population; one to seven studies were performed for each patient. These included 95 head CT studies, two orbital CT studies, 11 spinal CT studies, four cranial MR studies, four spinal MR studies, and seven myelographic studies. Each study was reviewed independently by three radiologists with knowledge of the patient's age and clinical history. The radiologic findings were categorized on the basis of agreement between two or more of the reviewers. The data from the study were analyzed in terms of neuroimaging findings, clinical presentations, indications for neuroradiologic studies, and resultant therapy.

Results

The radiologic findings are summarized in Table 1. Twenty patients were noted to have CNS metastases including 11 with intracranial metastases, eight with spinal lesions, and one with both brain and spinal metastases. The overall rate of CNS metastases in all 299 patients was 6.7%. Seven (2.3%) of the 299 patients initially presented with CNS metastases. This group included three patients with brain metastases and four patients with spinal metastases. All had extensive metastatic involvement elsewhere, most frequently to the lungs and/or retroperitoneum. Of the 13 patients who presented later in their disease course with CNS metastases, all were in advanced stages with the exception of two patients with localized primary mediastinal disease. The sites of origin of the eight spine metastases were the testis in six patients, the mediastinum in one patient, and the retroperitoneum in one patient. Of the 11 patients with brain metastases, eight had testicular and three had mediastinal primary tumors. The patient with both brain and spine metastases had a testicular primary. At the time of diagnosis of brain metastases, all nine testicular cancer patients and two of three primary mediastinal tumor patients had prior or concomitant pulmonary metastases.

The location of the intracranial metastases was predominantly supratentorial ($n = 7$). However, a significant number were also located infratentorially ($n = 2$) or in both locations ($n = 3$). One patient who had multiple intracranial metastases also had a concomitant retinal metastasis. Multiple brain metastases were seen in five patients and hemorrhagic brain metastases were noted also in five patients. Three patients developed obstructive hydrocephalus resulting from cerebellar metastases (Fig. 1).

The nine spinal metastases were equally divided between epidural, bone, and combined involvement (Figs. 2 and 3). Epidural involvement was associated with mediastinal ($n = 2$) or retroperitoneal ($n = 3$) masses in five of six patients. One of the mediastinal masses was the primary tumor; the other four masses were due to distal nodal metastases. Four of the patients with bone invasion developed vertebral compression fractures. Involvement of a solitary vertebral level was not

TABLE 1: Neuroimaging Findings in Patients with Germ Cell Neoplasms

Finding	No. of Patients
CNS metastases	
Intracranial	
Supratentorial	7
Infratentorial	2
Both	3
Spinal	
Epidural	3
Bone	3
Epidural and bone	3
Subtotal	20[a]
Atrophy	
Focal	3[b]
Diffuse	13
Subtotal	16
Ventriculomegaly only	2
Questionable abnormality	4
Normal	24
Total	66

[a] One patient had both spinal and intracranial metastases.
[b] Includes one patient with cerebellar atrophy.

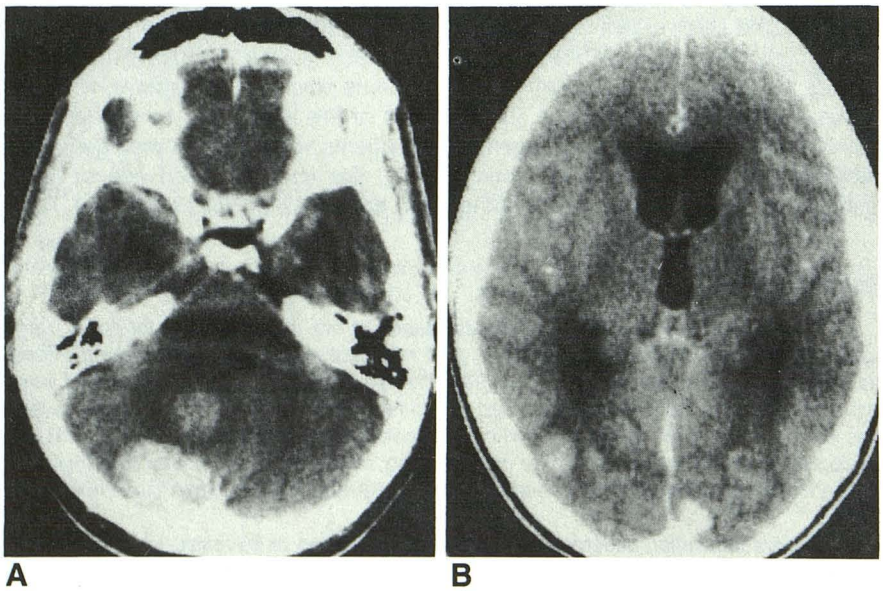


Fig. 1.—Brain metastases from testicular carcinoma in 19-year-old man.
***A*, Contrast-enhanced CT scan shows cerebellar metastases with mass effect compressing fourth ventricle.**
***B*, Image at more superior level shows multiple enhancing supratentorial metastases and obstructive hydrocephalus.**

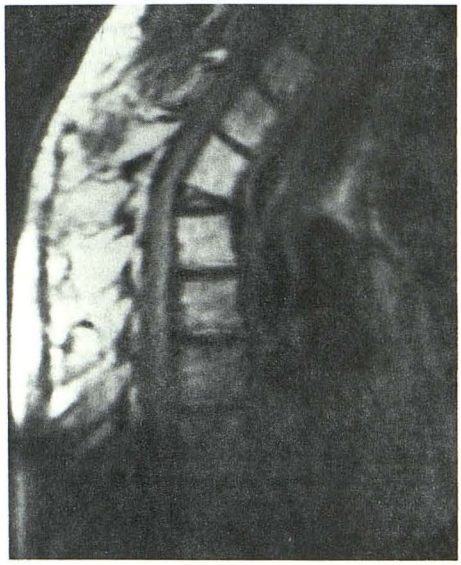
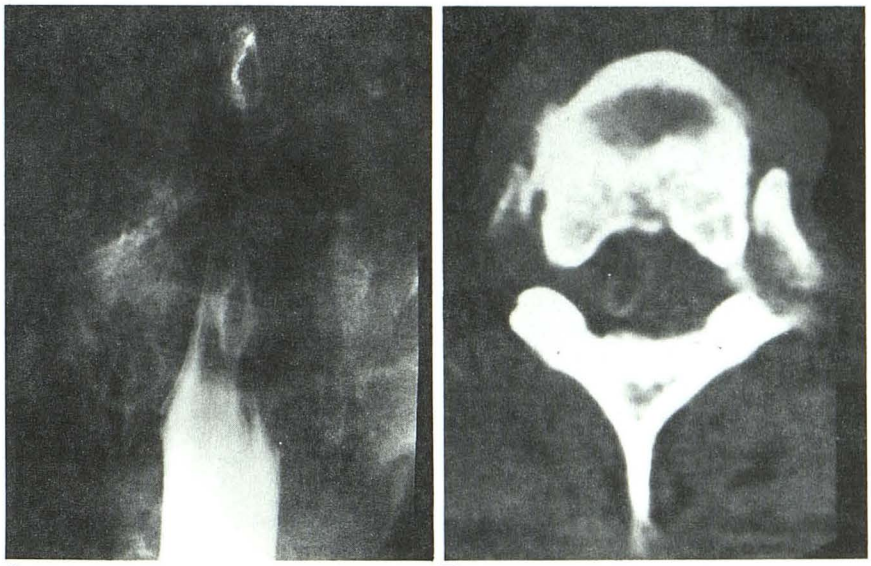


Fig. 2.—Vertebral body metastasis. Sagittal spin-echo MR image, 1500/20 (TR/TE), of thoracic spine shows compression fracture of third thoracic vertebral body due to metastasis in patient who initially presented with back pain and testicular mass.



A B

Fig. 3.—Thoracic spine metastasis in 30-year-old testicular cancer patient with lower extremity paralysis.
A, Thoracic myelogram shows extradural mass effect with nearly complete myelographic block.
B, Postmyelogram CT scan shows metastasis to T4 vertebral body with epidural extension and spinal cord compression.

uncommon and was noted in six of the nine patients. Five patients had evidence of cord compression on CT, MR, or myelography.

The frequencies of CNS metastases due to various types of germ cell tumors are listed in Table 2. There was a similar distribution of histologic types in patients with CNS metastases and in the total population undergoing CNS imaging. A majority of patients imaged and of patients with CNS metastases had mixed germ cell tumors.

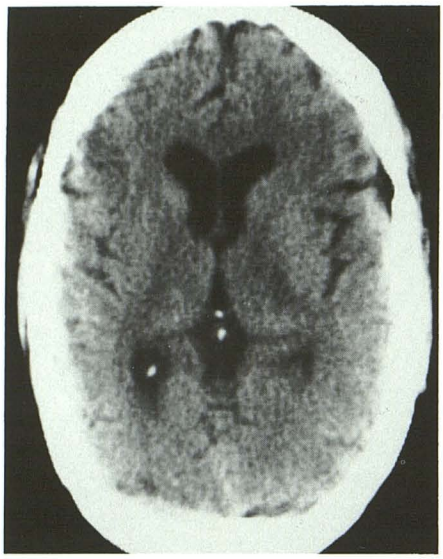
Sixteen patients had either diffuse or focal cerebral atrophy and/or cerebellar atrophy. Mild to moderate diffuse cerebral atrophy was noted in 13 patients, as manifested by ventriculomegaly and sulcal and cisternal prominence (Fig. 4). None of these patients had prior cranial irradiation or symptoms of communicating hydrocephalus. All but two patients with diffuse atrophy had received varying amounts of systemic combination chemotherapeutic regimens composed of *cis*-platinum, bleomycin, and either etoposide or vinblastine. Focal atrophy was described as localized prominence of the sylvian fissures in two cases and as cerebellar atrophy in a third. The latter patient had no clinical signs of cerebellar dysfunction or history of alcohol abuse, phenylhydantoin therapy, or other predisposing factors. In addition, moderate ventricular enlargement was seen in two patients with normal cortical sulci and no clinical symptoms or signs of hydrocephalus (Fig. 5). Ventriculomegaly in these patients may have been due to central parenchymal loss, but hydrocephalus could not be excluded entirely.

In addition to patients with metastases and atrophy, four patients had questionable abnormalities that were never confirmed; the remaining 24 patients had normal studies.

TABLE 2: Germ Cell Tumor Histologies in Patients Requiring Neuroimaging and Patients with CNS Metastasis

Histology	No. (%)	
	Undergoing Neuroimaging	With Metastasis
Mixed germ cell tumor	39 (59.1)	12 (60)
Embryonal carcinoma	8 (12.1)	1 (5)
Choriocarcinoma	3 (4.5)	2 (10)
Yolk sac tumor	4 (6.1)	2 (10)
Seminoma	3 (4.5)	0 (0)
Malignant teratoma	1 (1.5)	0 (0)
Teratocarcinoma	1 (1.5)	0 (0)
Unknown	7 (10.6)	3 (15)
Total	66	20

The indications for neuroimaging are listed in Table 3 for patients with CNS metastases and in Table 4 for patients without CNS metastases. Focal neurologic deficits were noted in 17 patients and led to imaging, which detected metastases in 15, an unconfirmed questionable abnormality in one, and atrophy in another patient. The deficits in these latter two patients were transient and resolved within 24 hr. All patients with brain metastases had neurologic deficits. Eight patients with spinal metastases had presented with spinal pain; four of these had an associated neurologic deficit. Not listed in Table 3 is the fact that three patients with metastases had seizures in addition to their focal neurologic deficits. Overall, three of six patients with seizures had brain metastases. In 25 neurologically asymptomatic patients, head



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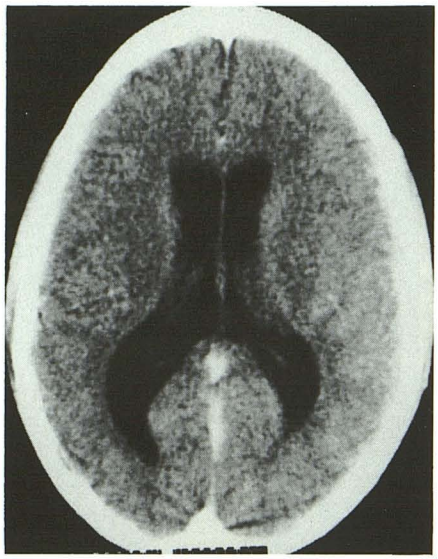

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Fig. 4.—Cerebral atrophy. Noncontrast head CT scan in 35-year-old testicular cancer patient shows diffuse cerebral atrophy representative of that seen in our study.

Fig. 5.—Ventriculomegaly. Noncontrast CT scan in 17-year-old testicular cancer patient shows ventriculomegaly without sulcal prominence. There were no signs or symptoms of hydrocephalus, possibly because of central atrophy.

TABLE 3: Clinical Presentation of Patients with CNS Metastases

Location of Metastasis	No. of Patients
Intracranial	
Focal neurologic deficit	11
Focal neurologic deficit with coma	1
Subtotal	12
Spinal	
Back/neck pain with neurologic deficit	4
Back/neck pain without neurologic deficit	4
Asymptomatic radiographic metastasis[a]	1
Subtotal	9
Total	20[b]

[a] One patient was asymptomatic for 4 months before developing pain.
[b] One patient had both intracranial and spinal metastases.

TABLE 4: Indications for CNS Imaging in 46 Patients Without CNS Metastasis and Imaging Findings

Indication	No. of Studies with These Radiographic Findings		
	Normal	Atrophy	Questionable Abnormality
Headaches without neurologic deficit	8	3	1
Mental status changes	0	3	1
Eye pain	3	0	0
Seizures	1	2	0
Syncope	0	1	0
Focal neurologic deficit			
Transient unilateral ptosis and facial nerve palsy	0	0	1
Transient unilateral reduced vision	0	1	0
Fever—rule out abscess	1	0	0
Rule out sanctuary site	15	9	1
Low back pain without neurologic deficit	1	0	0
Drug-induced dystonic reaction	1	0	0
No clear indication	2	1	0

CT scans were obtained to detect occult brain metastases or "sanctuary sites" in the setting of elevated serum tumor markers (human chorionic gonadotropin–beta subunit and alpha-fetoprotein) following chemotherapy. Brain metastases were seen in none of these.

The clinical therapy after the diagnosis of brain or spinal metastases included a variety of therapeutic protocols. Nineteen of 20 patients received subsequent systemic chemotherapy. One patient with brain metastases was lost to follow-up. Ten of 12 patients with intracranial metastases received subsequent whole-brain radiation therapy; five underwent craniotomy for resection of a solitary metastasis in addition to radiation therapy. Three patients required emergency ventricular shunting for obstructive hydrocephalus. Of the nine patients with spinal metastases, six received local spinal radiation therapy and two underwent decompressive laminectomy. In another spinal metastasis patient, spinal stabilization rods were placed surgically.

Discussion

The most common site of origin of germ cell neoplasm in our patients was the testis. This is an uncommon malignancy overall, accounting for only 1% of malignancies in males. However, testicular cancer is important since it is the most common malignancy in young adult males and may result in significant loss of productive years in this age group [5]. Approximately 75% of patients achieve a complete response to *cis*-platinum–containing chemotherapy regimens and postchemotherapy surgery. The estimated probability that these patients will be free of disease at 12 years is nearly 85% [6]. Extragonadal germ cell neoplasms are even less

common than testicular cancer, but generally carry a poorer prognosis [5].

Although therapy for germ cell neoplasm is quite successful, in two large clinical series [3, 6] approximately 15% of the patients developed brain metastases some time during the course of their disease. Of the patients in our study, 2.3% initially presented with CNS metastases, but only 1.0% presented with brain metastases. Overall, 4% developed brain metastases during the course of their disease. This prevalence is much lower than the previously reported figure for at least three reasons. First, our follow-up has been for a much shorter interval than that in the other investigations. Second, because our institution is a referral center for these patients, many return to the care of their local physicians, sometimes resulting in incomplete follow-up. Third, our method of identifying patients who require neuroimaging by reviewing their radiology records at our medical center will fail to identify some patients who are studied at other institutions. Many of these studies are sent to us for review, but an unknown number are not.

An important characteristic of our population is that nearly all of our patients had nonseminomatous germ cell neoplasms (Table 2). This can be attributed to the fact that the majority of these patients are referred to our institution for treatment of advanced or refractory disease, which typically is nonseminomatous at histology. In addition, although seminomas account for 40% of testicular tumors [5], these tumors have a lower rate of CNS metastases than do other kinds of germ cell neoplasms [3]; therefore, neuroradiologic evaluation usually is not required.

The importance of identifying CNS metastases is that therapy is altered when these lesions are present. Radiation therapy was used in 80% of our patients, and orthopedic surgery or neurosurgery was used in 55% after brain or spinal lesions were discovered. The treatment philosophy at our medical center is to use radiation therapy in addition to standard chemotherapy when a patient has CNS metastases at the time of initial diagnosis. If a solitary CNS metastasis is the only manifestation of disease during a relapse, then surgical resection of the lesion is followed by chemotherapy and CNS irradiation. Surgery is not used when there are multiple metastases to the brain. Palliative cranial radiation therapy is often used in addition to chemotherapy in cases of CNS involvement associated with progressive neoplastic disease elsewhere [5].

Few MR studies were performed in our patients. MR was not performed with paramagnetic contrast material because Gd-DTPA was not clinically available when the studies were performed. A recent evaluation of 50 patients with suspected brain metastases found that Gd-DTPA–enhanced MR images were more sensitive for detecting intracranial metastases than contrast-enhanced CT scans were [7]. Nonenhanced MR was the least useful examination in this study because of a lack of specificity for discriminating metastatic lesions from ischemic or radiation changes. Since the identification of CNS metastases is very important in making treatment decisions for patients with germ cell tumors, future evaluation of these patients should be performed with Gd-DTPA–enhanced MR whenever clinically possible.

Brain metastases from germ cell neoplasms are thought to be spread hematogenously. Once malignant cells penetrate the lung they may enter the systemic circulation and involve the brain and other organs. Therefore, it is not surprising that in a study of 38 patients with brain metastases from testicular cancer, all had existing or preexisting pulmonary involvement [4]. In our nine patients with testicular cancer metastatic to the brain, pulmonary lesions were demonstrated also. However, one of the three patients with primary mediastinal germ cell tumors did not have lung metastases. Perhaps the tumor in this patient directly seeded the systemic arterial blood supply.

Although the leptomeninges are a site of metastases in some malignancies [8], carcinomatous meningitis was not found in germ cell tumor patients with brain metastases in one large series that specifically mentioned this entity [4], and it was not observed in our patients with intracranial metastases. Involvement of the leptomeninges also was not reported in an autopsy series of 78 patients with metastatic testicular carcinoma [2]. However, there was a case report of an acute subdural hematoma in a patient with testicular cancer metastatic to the dura [9]. Nevertheless, meningeal metastases from germ cell tumors originating outside the CNS appear to be uncommon.

The frequency of mild to moderate cerebral atrophy was unexpectedly high in our patients. Cerebral atrophy has been associated with intrathecal methotrexate [10, 11] but is not known to be associated with the systemic chemotherapeutic agents used to treat germ cell neoplasms. The patients at our institution are evaluated with histories, physical examinations, and a questionnaire [6], but no formal neuropsychological evaluation is performed routinely to determine if there are subtle deficits associated with the atrophy. There have been no controlled studies to determine whether or not the chemotherapeutic regimens in question have a causal relationship to cerebral atrophy. However, *cis*-platinum, the principal agent in combination chemotherapy for germ cell tumors, has well-documented neurotoxic effects including ototoxicity [10] and peripheral neuropathies [10, 12]. Although it is reported to cross an intact blood-brain barrier (BBB) poorly during IV therapy, a disrupted BBB, perhaps from subclinical metastases that are later ablated by the chemotherapy, will allow significant drug concentrations in the CNS [10, 13]. IV *cis*-platinum after BBB disruption has produced necrosis and hemorrhagic infarction of cerebral tissue in dog models [14]. In addition, combination chemotherapy with bleomycin, *cis*-platinum, and vinblastine has been associated with vascular toxicities that include acute cerebrovascular accidents [15]. Although no direct causal relationship has been shown, the potential for subclinical CNS toxicity as manifested by cerebral atrophy may exist. Two of the 16 patients with atrophy had not received chemotherapy before head CT studies, which suggests factors other than chemotherapy can be involved in the development of cerebral atrophy. There has been a report of cortical cerebellar degeneration occurring in conjunction with testicular neoplasm, presumably as a result of a paraneoplastic process [16]. However, to our knowledge there has been no description of diffuse atrophy resulting from a systemic effect of neoplasms. In one patient in our study,

cerebellar atrophy was demonstrated on CT, but the neurologic deficits typically associated with cortical cerebellar atrophy were not present.

The indications for neuroimaging in our patients were evaluated to determine if guidelines could be developed for the efficacious use of radiologic studies. The presence of neurologic deficits and spine pain with or without neurologic deficits were the indications with the highest yield of positive examinations and are valid indications for imaging. However, many cancer patients with metastatic retroperitoneal lymphadenopathy have back pain and are not referred for spine imaging. The high percentage of positive spinal examinations in our study was likely due to the referral of patients with predominantly neurologic and/or positive plain film findings. Evaluation of seizures detected brain metastases in half the patients with this presentation; therefore, seizures are a useful indication for imaging. Examination of headaches without focal deficits detected no finding that altered therapy in these patients. Of 25 patients who were studied to rule out occult lesions, none had brain metastases. Therefore, screening the CNS in neurologically asymptomatic patients with unexplained elevations of serum tumor markers does not appear to be clinically useful.

In conclusion, the presence of CNS metastases significantly alters therapy in patients with germ cell tumors. Neuroradiologic studies are most useful in the presence of neurologic deficits, significant back pain, and recently developed seizures. However, screening neurologically asymptomatic patients with unexplained elevations of serum tumor markers for occult CNS lesions detected no metastases and is not recommended. Since Gd-DTPA–enhanced MR has greater sensitivity than other commonly used techniques [7], it should be the imaging technique of choice in screening germ cell tumor patients for CNS metastases. In addition, neuroimaging revealed an unexpectedly frequent occurrence of cerebral atrophy in our patients. The functional significance and etiology of this is unclear and should be studied further.

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