5. Green DM, Brecher ML, Blumenson LE, Grossi M, Freeman AI. The use of intermediate dose methotrexate in increased risk childhood acute lymphoblastic leukemia. A comparison of three versus six courses. *Cancer* 1982, **50**, 2722–2727.
6. Evans WE, Huston PR, Stewart CR *et al.* Methotrexate cerebrospinal fluid and serum concentration after intermediate dose methotrexate infusion. *Cancer Pharmacol Ther* 1983, **33**, 301–307.
7. Ettinger LJ, Chervinsky DS, Freeman AI, Creaven PJ. Pharmacokinetics of methotrexate following intravenous and intraventricular administration in acute lymphocytic leukemia and non-Hodgkin's lymphoma. *Cancer* 1982, **50**, 1976–1682.
8. Bode U, Magrath IT, Bleyer A, Poplack DG, Glaubiger DL. Active transport of methotrexate from cerebrospinal fluid in humans. *Cancer Res* 1980, **40**, 2184–2187.
9. Hryniuk WN, Bertino JR. Treatment of leukemia with large doses of methotrexate and folinic acid: clinical biochemical correlates. *J Clin Invest* 1969, **48**, 2140–2155.
10. Shapiro WR, Young DF, Mehta BP. Methotrexate: distribution in cerebrospinal fluid after intravenous ventricular and lumbar injections. *N Engl J Med* 1975, **293**, 161–166.
11. Rosen G, Ghavimi F, Nirenberg A, Mosenda C, Mehta BM. High dose methotrexate with citrovorum factor rescue for the treatment of central nervous system tumors in children. *Cancer Treat Rep* 1977, **61**, 681–690.
12. Thyss A, Milano G, Deville A, Manassero J, Renee N, Schneider M. Effect of dose and repeat intravenous 24 hr infusions of methotrexate on cerebrospinal fluid availability in children with hematological malignancies. *Eur J Cancer Clin Oncol* 1987,**6**, 843–847.
13. Allen JC, Rosen G, Mehta BM, Horten B. Leukoencephalopathy following high-dose i.v. methotrexate chemotherapy with leucovorin rescue. *Cancer Treat Rep* 1980, **64**, 1261–1273.
14. Maurus R, Boilletot A, Otten J. Treatment of acute lymphoblastic leukemia in children with the BFM protocol; a cooperative study and analysis of prognostic factors. *Haematol Bood Transf* 1987, **30**, 466–470.
15. Langermann HJ, Henze G, Wulf M, Richm M. Abschatzung der Tumorzellmasse bei der akuten lymphoblastichen Leukamie im Kindesalter: prognostiche Bedeutung und praktische Anwendung. *Klin Pediatr* 1982, **194**, 209–213.
16. Imber M. Pignon J, Lena N. Enzymatic assay MTX, centrifugal analyser. *Clin Chem* 1983, **29**, 1317–1318.
17. Evans WE, Crom WR, Yalowich JC. Methotrexate. In: WE Evans, JJ Schentag, WI Jusko, eds. *Applied Pharmacokinetics*. Spokane, Applied Therapeutics, 1986, 1009–1056.
18. Borsi J, Moe PJ. A comparative study on the pharmacokinetics of methotrexate in a dose range of 0.5 g to 33.6 g/m^2 in children with acute lymphoblastic leukemia. *Cancer* 1987, **60**, 5–13.
19. Janka G, Mack R, Helmig M, Haas RJ, Bidlingmaier F. Prolonged methotrexate infusions in children with acute leukemia in relapse and in remission and with medulloblastoma. Pharmacokinetics, toxicity and clinical results. *Oncology* 1984, **41**, 225–232.
20. Lankelma J, Lippens RJJ, Drenthe-Schonk A, Termond EFS, van der Kleijn E. Change in transfer rate of methotrexate from spinal fluid to plasma during intrathecal therapy in children and adults. *Clin Pharmacokin* 1980, **5**, 465–475.
21. Thyss A, Milano G, Etienne MC *et al.* Evidence for CSF accumulation of 5-methyltetrahydrofolate during repeated courses of methotrexate plus folinic acid rescue. *Br J Cancer* 1989, **59**, 627–630.

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Early Diagnosis of Spinal Epidural Metastases Using Out-patient Computed Tomographic Myelography

Stuart A. Grossman, David E. Weissman, Henry Wang, Mark R. Gilbert, Marcia L. Updike, Valerie Walton and Moody Wharam

Twenty patients with known malignancies, back pain, abnormal roentgenograms of the spine, and normal neurological examinations were evaluated by outpatient computed tomographic (CT) myelography to determine the presence and extent of epidural tumor. Spinal CT following the intrathecal administration of low doses of water soluble contrast agents provided high quality diagnostic information. Three patients experienced adverse effects from this procedure which were mild and easily managed in the outpatient setting. Epidural tumor was identified in 15 of 20 (75%) patients. Patients were followed for 9–27 months following myelography. The 14 patients with epidural tumor treated with local radiation experienced pain relief and only one of these patients developed signs or symptoms of recurrent epidural tumor in the treated site. This study documents the high incidence of epidural tumor in selected patients without neurological deficits and the excellent palliative results of non-emergent, carefully planned radiation therapy. It also demonstrates that high resolution CT myelography can be performed safely in an outpatient setting in patients at high risk for epidural tumor. Outpatient myelography facilitates the early diagnosis of epidural tumor and provides needed information on the extent of the tumor for radiation treatment planning while conserving health care resources. For these reasons, outpatient CT myelography should be considered in selected patients with cancer who are at high risk for epidural metastases.
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INTRODUCTION

SPINAL EPIDURAL metastases are a common complication of cancer and are usually regarded as an oncologic emergency [1, [2]. Early diagnosis and treatment of these lesions provides excellent pain relief and prevents the development of permanent neurologic deficits [1–6]. Patients are generally admitted to the hospital specifically for this procedure to confirm the presence and to document the extent of epidural tumor. Many factors associated with myelography, such as hospitalization, cost, and time away from home or work encourage physicians and patients to postpone this important diagnostic study until severe pain, neurologic deficits and an oncologic emergency are present.

This manuscript reports the results of a prospective trial designed to establish the safety and efficacy of outpatient myelography in patients at high risk for epidural tumor. In addition, this study sought to confirm the high incidence of epidural metastases in this patient population with cancer, back pain, abnormal roentgenograms of the spine, and normal neurological examinations.

PATIENTS AND METHODS

Twenty patients were entered on a protocol approved by the Joint Committee on Clinical Investigations at the Johns Hopkins Hospital to determine the feasibility of outpatient CT myelography in patients at high risk for epidural spinal cord compression and to confirm the high incidence of epidural metastases in these patients. Patients eligible for participation in this study had metastatic cancer, back pain presumed to be secondary to cancer, an abnormal spine roentgenogram (compression fractures, lytic or blastic lesions, or loss of a pedicle), and a normal neurological examination. Each also had a responsible adult who would stay with the patient for 24 h following myelography. Patients were evaluated in the outpatient department and eligible patients were scheduled for elective outpatient CT myelography within 1 week of their initial visit. Neurological examinations were performed by the participating neurologist (M.R.G.) and spine roentgenograms were reviewed by faculty in the Division of Neuroradiology. Phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants were discontinued for 48 h prior to and 24 h after the procedure. Patients were orally hydrated the day prior to the procedure. Intravenous hydration, atropine (0.4 mg i.m.) and diazepam (10 mg p.o.) were administered and baseline neurologic status and vital signs were recorded immediately prior to the procedure.

Cervical or lumbar puncture was performed in the neuroradiology suite under fluoroscopic guidance using a 25 gauge spinal needle. Three hundred to 600 mg of iodine were injected into the subarachnoid space when metrizamide (Winthrop-Breon Laboratories, New York, NY) was used and of 600 mg iodine were administered when the contrast agent was Iopamidol (Squibb Diagnostics, New Brunswick, NJ) or Iohexal (Winthrop-Breon Laboratories, New York, NY). Axial CT scans (4 mm slice thickness and 4 mm table increment contiguous sections) were taken above, through, and below all vertebral levels where skeletal roentgenograms were abnormal. In addition, the entire region of interest (cervical, thoracic or lumbar spine) was sampled by obtaining a single axial scan through each vertebral body at the level of the pedicles. Conventional film screen myelography was not performed.

All patients were observed for a minimum of 1 h in the Oncology Center's Outpatient Department upon completion of the procedure. Steroids and radiation therapy were initiated following myelography if indicated. Patients were discharged in the care of a companion to be observed for 24 h and were encouraged to keep their head elevated during the observation period. They were contacted by telephone the day following the myelogram to determine if headache, nausea, vomiting, worsening of neurologic status, visual or auditory hallucinations, speech disturbances, disorientation, depression, seizures, or feelings of depersonalization were noted. Inpatient and outpatient medical records of patients on this study were reviewed to determine their response to treatment and the clinical course of their malignancy.

RESULTS

Twenty outpatients at high risk for epidural metastases were evaluated with intrathecally enhanced CT scans. These patients ranged in age from 38–70 (average 56), 16 were female, and 14 had metastatic breast cancer (Table 1). Back pain was reported for an average of 3.2 weeks (range 1–12) prior to CT myelography. Eighteen patients underwent lumbar myelography while two were studied using the cervical approach. Eighteen studies were performed using metrizamide, one using Iopamidol and one using Iohexol. CT scans were obtained through an average of 12 vertebral levels (range 7–24) in each patient.

Adverse effects from this procedure were mild and uncommon. One patient developed a headache which responded to 500 mg of acetaminophen and two patients had transient nausea and vomiting. No patient experienced worsening neurologic status, visual or auditory hallucinations, speech disturbances, disorientation, depression, depersonalization, or seizures and no patients required hospitalization following this procedure.

Fifteen of twenty CT myelograms (75%) demonstrated epidural metastases. In each case tumor extended into the epidural space from adjacent vertebral bodies which contained metastatic tumor (Fig. 1). Patients with positive studies had epidural tumor which extended an average of 5 vertebral levels (range 1–14). No patient had a complete block to the flow of contrast in the subarachnoid space and most patients had only a small amount of epidural tumor deforming the contrast filled subarachnoid space (Fig. 2). Three of the five patients who did not have epidural tumor had vertebral body metastases and the remaining two patients had vertebral compression fractures.

Fourteen of the 15 patients with epidural tumor received local irradiation and fourteen received dexamethasone. The administered doses of radiation therapy are shown in Table 1. Radiation was not given to patient #20 because he had previously received maximal irradiation to the site of his epidural tumor. His symptoms gradually progressed and he underwent an anterior decompression. Dexamethasone was not administered to patient #6 because of a prior episode of disseminated fungal infection with steroids. All patients treated for their epidural tumor noted improvement in back pain and maintained their normal neurologic status throughout the treatment period.

Patients entered on this research study were followed for 9–27 months following outpatient CT myelography. Six (30%)

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Table 1

Patient	Age	Sex	Tumor	Pain duration (weeks)	Cervical/ lumbar	Location of epidural cancer	Number of vertebral bodies scanned	Number of vertebral bodies with tumor	Radiation therapy dose (rads)	Survival (months)
1	55	F	Breast	5	L	L4	16	1	3000	> 27
2	70	F	Breast	2	L	T3–L3	16	13	3000	22
3	54	F	Breast	3	L	T9	9	1	3000	5
4	59	F	Breast	4	L	T8–L3	24	8	2500	16
5	65	F	Breast	2	L	T8–11, LI	12	5	2500	9
6	55	F	Breast	7	L	C3	9	1	3000	> 25
7	54	F	Breast	1	C	L2–4	5	3	3000	22
8	38	F	Breast	2	L	T12	11	1	3000	> 18
9	62	F	Lung	8	C	None	9	0	None	12
10	52	F	Breast	3	L	C7	7	1	3000	10
11	49	F	Breast	8	L	T1–2, T10–12	17	5	2700	> 17
12	50	F	Breast	1	L	T5–12, L2–4	14	11	1440	3
13	55	F	Breast	3	L	None	7	0	2000	2
14	55	F	Breast	2	L	T9–11	9	3	3000	12
15	63	M	Lung	12	L	None	9	0	None	7
16	53	M	Esophagus	2	L	None	17	0	3000	2
17	58	F	Breast	1	L	T11, L3–4	18	3	2700	11
18	60	M	Lung	1	L	None	8	0	3000	> 10
19	60	F	Lung	4	L	T2–L3	16	14	3000	13
20	51	M	Salivary	3	L	T3–9	9	7	None	> 9

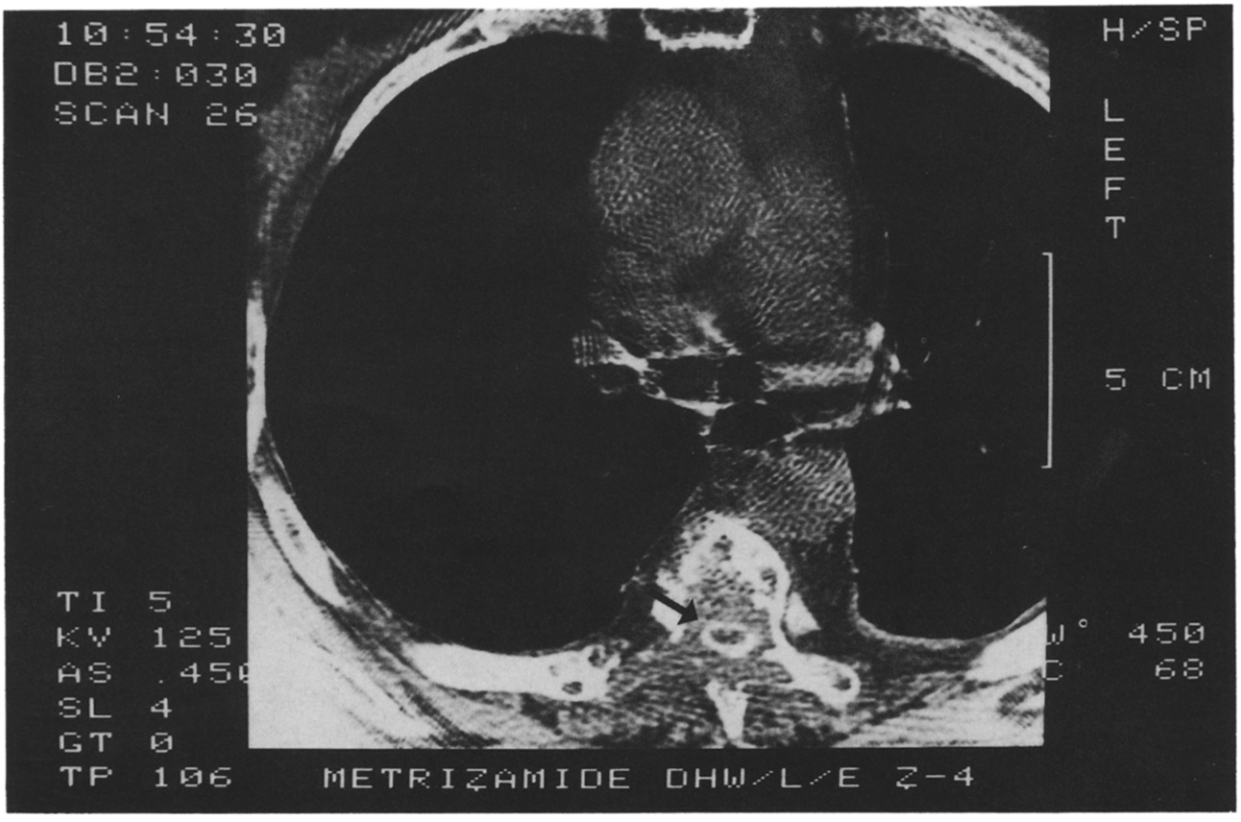

Fig. 1. Out-patient CT myelography in patient #3 reveals extensive destruction of T5 with epidural tumor (arrow) surrounding the contrast filled subarachnoid space.

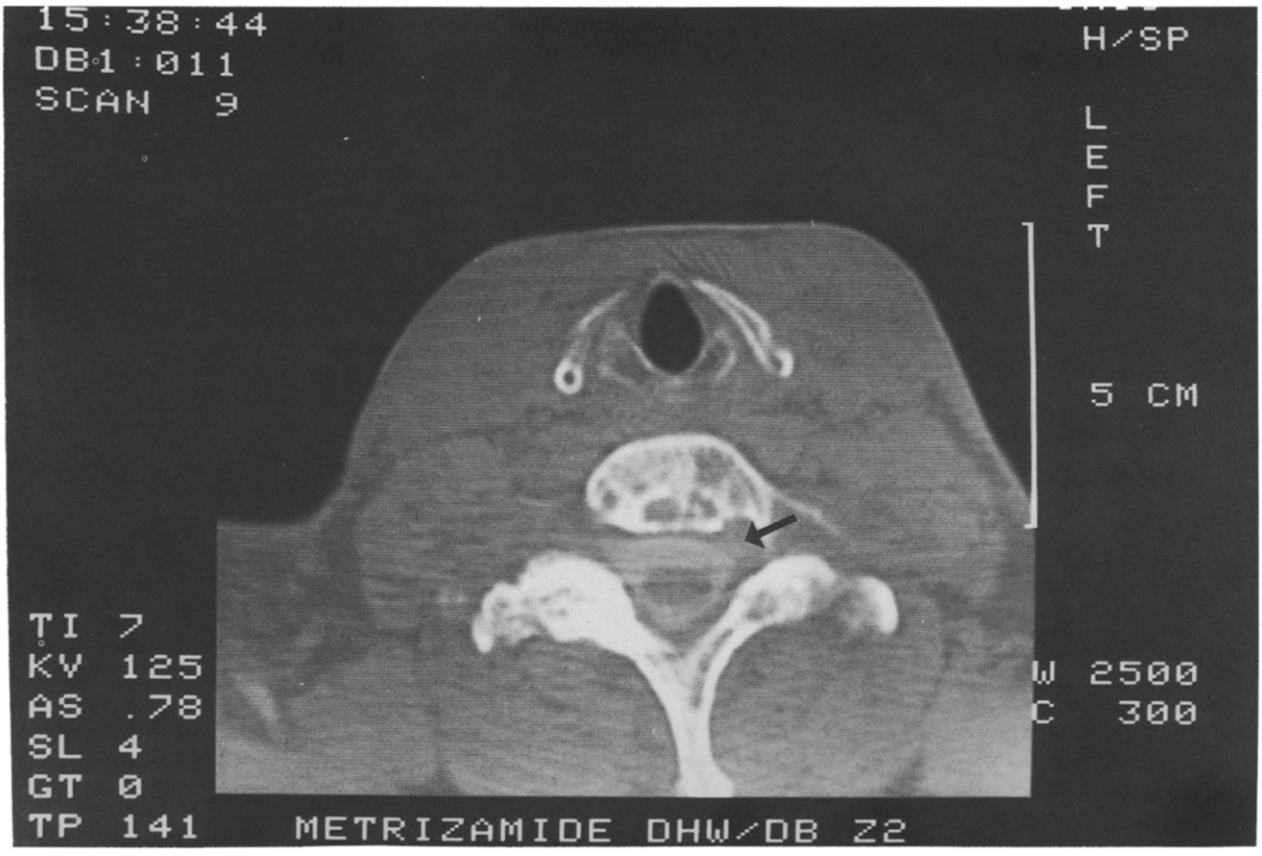

Fig. 2. Epidural tumor (arrow) is noted to deform the contrast filled subarachnoid space at the level of C7 in patient #10.

remained alive an average of 14 months (range 9–27) following the demonstration of epidural tumor while 13 patients died of progressive tumor an average of 9 months (range 2–22) following CT myelography. Only one patient (#6) treated with local radiation therapy recurred in the irradiated site. This occurred 22 months after initial treatment. She remains neurologically normal following surgical decompression and anterior and posterior fixation of the spine.

DISCUSSION

Spinal epidural metastases are a common complication of cancer. Patients with epidural tumor usually present with back or radicular pain that persists for weeks before neurologic signs or symptoms develop. [1–6]. However, once neurologic deficits are noted they may progress rapidly and ultimately lead to irreversible loss of neurologic function. Many patients with cancer and back pain are treated with analgesics and followed clinicaly until neurologic signs and symptoms develop. In recent series approximately 50% of patients have significant neurologic deficits before the diagnosis of epidural tumor is made and appropriate therapy is initiated [1–6]. The degree of neurologic disability at the time when therapy is initiated is a major predictive factor in the ultimate functional status of patients [1–6]. Many patients with cancer and back pain are currently given analgesics and followed clinically until neurological signs and symptoms develop. Others are empirically irradiated for pain control without determining if tumor is present in the epidural space or evaluating the caudal and rostral extent of epidural tumor. Studies have demonstrated that cranio-caudal extension of tumor in the epidural space and synchronous non-contiguous epidural metastases are common and that treatment planning without meylography can result in inadequate radiation therapy ports [7–8].

Early diagnosis and treatment of epidural tumor is fundamental to providing optimal pain control and preservation of neurologic function. There are two basic mechanisms whereby patients can develop epidural metastases [1, 2, 5, 6]. The first results from direct extension of tumor through the intervertebral foramina. This is most common in patients with lymphomas and other posterior mediastinal or retroperitoneal masses and can be associated with normal bone roentgenograms. Epidural cord compressions may also develop from tumor which metastasizes to the vertebrae. As these lesions expand they may erode into the epidural space. Although bone scintography or high resolution computed tomography could identify patients with subtle vertebral tumor which could be associated with epidural metastases, it is impractical to fully evaluate all patients with metastatic malignancies who have some degree of vertebral involvement. Furthermore, it has been shown that vertebral lesions which are too small to be identified on plain spine roentgenograms are unlikely to have local tumor extension from the vetebral body into the epidural space [5]. In addition, patients with back pain, normal neurological examinations, and abnormal plain spine roentgenograms usually have a modest amount of epidural tumor which does not obstruct the flow of spinal fluid and responds well to conservative management [5].

This study demonstrates that high resolution CT myelography can be performed safely in patients with cancer, back pain and normal neurological examinations in an outpatient setting. It

also documents the high incidence of epidural tumor in these patients and the low risk of subsequent neurologic compromise in patients who receive non-emergent, carefully planned radiation therapy for early epidural lesions. Myelography to study the presence and extent of epidural tumor is usually performed on patients hospitalized for this procedure. However, patients with benign disorders have been evaluated with outpatient myelography using water soluble contrast media for the past decade and several studies have shown that myelography in ambulatory patients is associated with fewer side effects than it is in hospitalized patients kept at bed rest [9–14]. Computed tomographic myelography was described by DiChiro and Schellinger in 1976 [15]. This technique is accurate when compared to film screen myelography and is performed with lower doses of intrathecal contrast agents [16, 17]. As the neurotoxicity of water soluble contrast agents is largely dose related, CT myelography has a lower complication rate than standard myelography [17, 18].

Magnetic resonance (MR) imaging of the spine is a newer and non-invasive technique which can also be used on an outpatient basis to assess the presence of tumor in the epidural space [19]. Although the sensitivity and specificity of MR imaging and CT myelography have not been rigorously compared, both techniques would be expected to identify advanced epidural lesions. The sensitivity of MR imaging, with and without contrast, in the identification of small epidural tumor deposits must be carefully evaluated before this becomes the diagnostic test of choice in the detection of early epidural metastases. Preliminary data suggest that CT myelography may be more sensitive than MRI in defining small epidural lesions and outlining tumor margins in the epidural space [20]. Widespread availability of CT scanners, local expertise in myelographic techniques, and the development of less toxic water soluble contrast agents make it likely that CT myelography will remain a commonly used diagnostic test for the early detection of epidural tumor. Patients with cancer, back pain, abnormal spine roentgenograms, and normal neurologic examinations are ideal candidates for outpatient CT myelography. It has been demonstrated in this study and in that of Rodichock *et al.* [5] that these findings are associated with a high incidence of epidural metastases but rarely with tumor completely obstructing the flow of cerebrospinal fluid. Thus, these patients are at low risk for major changes in local CSF dynamics and neurologic deterioration following myelography. In addition, patients with a limited number of involved, preferably contiguous, vertebral bodies should be selected for evaluation using this technique. This permits the administered dose of contrast and the time required for CT scanning to be kept to a minimum.

Outpatient CT myelography facilitates the early diagnosis of epidural tumor and provides needed information on the extent of the tumor for radiation treatment planning while conserving the resources of the patient and the health care system. The combination of early myelography and careful treatment planning can be expected to provide optimal treatment for pain secondary to epidural tumor and to reduce the number of patients with cancer and back pain who develop potentially irreversible deterioration in neurologic function. For these reasons, outpatient CT myelography should be considered in selected patients with cancer who are at high risk for epidural metastases.

1. Gilbert RW, Kim J-H, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol* 1978, **3**, 40–51.
2. Posner JH. Management of central nervous system metastases. *Semin Oncol* 1977, **4**, 81–89.
3. Bruckman JE, Bloomer WD. Management of spinal cord compression. *Semin Oncol* 1978, **5**, 135–140.
4. Pedersen AG, Bach F, Melgaard B. Frequency, diagnosis, and prognosis of spinal cord compression in small cell bronchogenic carcinoma: review of 817 consecutive patients. *Cancer* 1985, **55**, 1818–1822.
5. Rodichok LD, Harper GR, Ruckdeschel JC *et al.* Early diagnosis of spinal epidural metastases. *Am J Med* 1981, **70**, 1181–1188.
6. Rodriguez M, Dinapoli RP. Spinal cord compression: with special reference to metastatic epidural tumors. *Mayo Clin Proc* 1980, **55**, 442–448.
7. Harper G, Cooper G, Rodichok L *et al.* Value of myelography for planning radiation treatment of spinal epidural metastases. (Abstr.) *Proc Am Soc Clin Oncol* 1984, **3**, 5.
8. Weissman DE, Gilbert M, Wang H, Grossman SA. The use of computed tomography of the spine to identify patients at high risk for epidural metastases. *J Clin Oncol* 1985, **3**, 1541–1544.
9. Kausch W. Myelography conducted on an outpatient bases. *Roentgenblaetter* 1981, **34**, 91–93.
10. Kostiner AI, Krook PM. Outpatient lumbar myelography with metrizamide. *Radiology* 1985, **155**, 383–385.
11. Kushner J, OBrien D, Croft V. Outpatient myelography in community hospitals (letter). *Neurosurgery* 1983, 13, 105.
12. Robertson WD, Lapointe JS, Nugent RA *et al.* Positioning of patients after metrizamide lumbar myelography. *Am J Radiol* 1980, **134**, 947–948.
13. Sykes RH, Wasenaar W_2 Clark P. Incidence of adverse effects following metrizamide myelography in nonambulatory and ambulatory patients. *Radiology* 1981, **138**, 625–627.
14. Van Niekerk JP. Myelography using water-soluble contrast media as an outpatient procedure. *S Afr Med J* 1979, **55**, 550–551.
15. DiChiro G, Schellinger D. Computed tomography of spinal cord after lumbar intrathecal introduction of metrizamide: computed assisted myelography. *Radiology* 1976, **120**, 101–104.
16. Dublin AB, McGahan JP, Reid MH. The value of computed tomographic metrizamide myelography in the neuroradiological evaluation of the spine. *Radiology* 1983, **146**, 79–86.
17. Zinreich SJ, Wang H, Updike ML *et al.* CT myelography for outpatients: an inpatient/outpatient pilot study to assess methodology. *Radiology* 1985, **157**, 387–390.
18. Hurwitz SR, Suyam M, Steinberg A. Aspiration of metrizamide following lumbar myelography. *Radiology* 1980, **136**, 789–790.
19. DiChiro G, Doppman JL, Dwyer AJ *et al.* Tumors and arteriovenous malformations of the spinal cord: assessment using MR. *Radiology* 1985, **156**, 689–697.
20. Hagenau C, Grosh W, Carrie M, Wiley RG. Comparison of spinal magnetic resonance imaging and myelography in cancer patients. *J Clin Oncol* 1987, 5, 1663–1669.