AJNR

# Limited Value of CT Brain Scans in the Staging of Small Cell Lung Cancer

David H. Johnson, Wayne W. Windham, Joseph H. Allen and F. Anthony Greco

# Limited Value of CT Brain Scans in the Staging of Small Cell Lung Cancer

David H. Johnson[1]
Wayne W. Windham[2]
Joseph H. Allen[2]
F. Anthony Greco[1]

Computed tomography of the brain was performed as part of the initial staging evaluation of 84 patients with small cell lung cancer. Brain scans indicative of metastatic disease were obtained in 12 (14%) patients, two of whom had no neurologic signs or symptoms. One of these had no other extrathoracic disease. Brain scans without evidence of metastatic disease were obtained in 72 patients, 58 (80.5%) of whom had no signs or symptoms suggestive of metastatic intracranial disease. In the 14 patients with neurologic symptoms but negative computed tomographic scans, other explanations than brain metastases were found. It was concluded that head scanning is a sensitive and accurate method of detecting central nervous system metastases in patients with small cell lung cancer. However, head computed tomography should not be included as part of the initial staging evaluation of the neurologically asymptomatic patients. In only one of 60 such patients did the brain scan change the initial clinical staging, which included chest films, liver and bone scans, and bone marrow biopsy.

About two-thirds of patients with small cell carcinoma (SCC) of the lung have detectable metastatic disease at the time of diagnosis [1]. Within this group, intracranial metastases are found during initial evaluation in 10%–14% [2, 3] and ultimately occur in 30%–65% in some autopsy series [4, 5]. To date, most SCC clinical trials have used the radionuclide brain scan as a noninvasive means of detecting brain metastases [6]. Although valuable in neurologically symptomatic patients [7], the radionuclide scan has not proved useful as a screening procedure in asymptomatic patients with lung cancer regardless of histologic classification [8–10].

Computed tomography (CT) of the brain is a more sensitive method of detecting cerebral metastases than is the radionuclide brain scan [11–13]. Consequently, head CT is frequently used as a screening procedure in the staging evaluation of asymptomatic patients with all histologic types of lung cancer including SCC. However, the usefulness of the CT brain scan in the latter role has yet to be determined [6, 14]. We reviewed our experience with head CT scans obtained as part of the initial pretreatment staging evaluation in 84 SCC patients seen at Vanderbilt University Medical Center. The results are the subject of this report.

## Materials and Methods

Eighty-four patients (average age 58.8 years; range 36–79 years; 65 men, 19 women) with SCC histologically or cytologically confirmed by our pathology department were the subjects of this study. All patients were evaluated at the Vanderbilt University Medical Center. Two patients had mixed tumors, one with SCC-adenocarcinoma and one with SCC–squamous cell carcinoma. Neither of the latter patients experienced a brain metastasis. In addition to brain scans, each patient underwent a staging evaluation that included a history and physical examination, chest film, complete blood cell count, screening blood chemistries, radionuclide liver and bone scans, and bilateral posterior iliac crest bone

TABLE 1: **Results of Staging Procedures, All Patients**

| Study | No. Tested | No. Positive (%) |
|---|---|---|
| Chest film | 84 | 83 (99) |
| Head CT scan | 84 | 12 (14) |
| Radionuclide liver scan | 80 | 22 (28) |
| Radionuclide bone scan | 80 | 24 (30) |
| Bone marrow aspiration/biopsy | 83 | 18 (22) |

marrow aspiration and biopsies. The results are given in table 1.

All CT images were obtained on either a first generation 60 sec translate-rotate EMI-1005 or a third generation 10 sec Omni 6000 scanner [15]. No fewer than eight adjacent 8 mm (EMI 1005) or 10 mm (Omni 6000) axial sections (about 20° with the canthomeatal line) were taken from the base to the apex of the skull, with special attention being paid to the posterior fossa and highest vertex cuts. All patients were imaged both before and after intravenous contrast enhancement with 50 ml of iothalamate meglumine 60% infused as a bolus immediately before imaging, followed by a rapid drip infusion during imaging of diatrizoate meglumine 30% or iothalamate meglumine 30%. Hard copy images were routinely obtained at a window level of 40 and a window width of 200 Hounsfield units (H).

All CT brain scans were reviewed retrospectively by two of the authors (W. W. W. and D. H. J.) without prior knowledge of any of the clinical or laboratory findings of the patients. The scans were interpreted in the following manner: (1) normal, no evidence of metastatic disease; (2) abnormal, compatible with metastasis; and (3) abnormal due to a nonmalignant pathologic process. For the purposes of this study, groups 1 and 3 are reported together. The CT criteria for metastasis were essentially the same as those used by Jacobs et al. [16], with some modifications, and included: (1) primary, direct visualization of a more or less well circumscribed, discrete area of abnormal density; (2) secondary cerebral edema, mass effect with distortion, or collapse of spaces (e.g., ventricles) and shift of midline structures; and (3) multiple lesions. The neurologic examination was judged normal if a neurologic review of systems was negative and a screening neurologic examination, as described by Wittes and Yeh [9] and modified by us, proved normal (namely, deep tendon reflexes, plantar response, frontal lobe signs, cranial nerves, funduscopic examination, and assessment of gait and mental status).

## Results

On the basis of the CT findings, the 84 SCC patients were divided into two groups: (1) patients with positive CT brain scans suggestive of metastatic disease, 12 (14%) patients and (2) patients with negative CT brain scans or with abnormalities that were clearly not metastatic in origin (e.g., cerebral atrophy), 72 (86%) patients. The mean age of group 1 patients was 62 years (range, 49–77 years) as compared with a mean age of 58 years (range, 36–79 years) in group 2.

Two group 1 patients were neurologically asymptomatic. Both had multiple lesions on CT (figs. 1 and 2). Of the other 10 symptomatic patients, the CT abnormality correlated with the clinical neurologic findings in eight. Two patients had neurologic symptoms suggestive of an intracranial metastasis that was confirmed by CT but failed to correlate with the specific clinical findings (e.g., one patient had cerebellar signs bilaterally but a single right insular lesion). Thus, 10 of the 12 patients with positive CT scans had clinical findings that indicated the presence of intracranial metastatic disease, the specific location of which was predictable on the
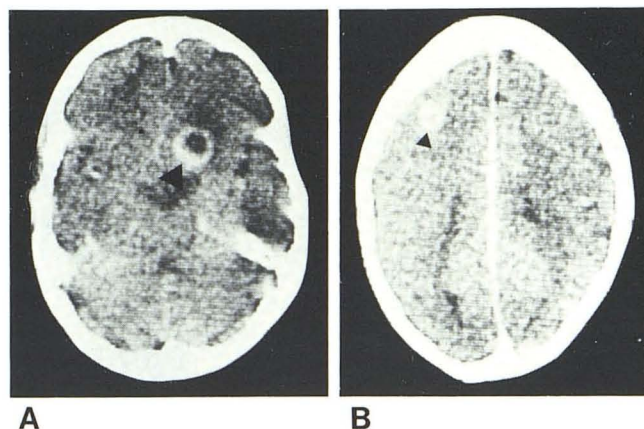


Fig. 1.—Neurologically asymptomatic patient with SCC. **A,** Contrast enhanced lesion (*arrowhead*) in right frontal area just below right frontal horn. **B,** Smaller lesion (*arrowhead*) higher in left frontal lobe anteriorly.
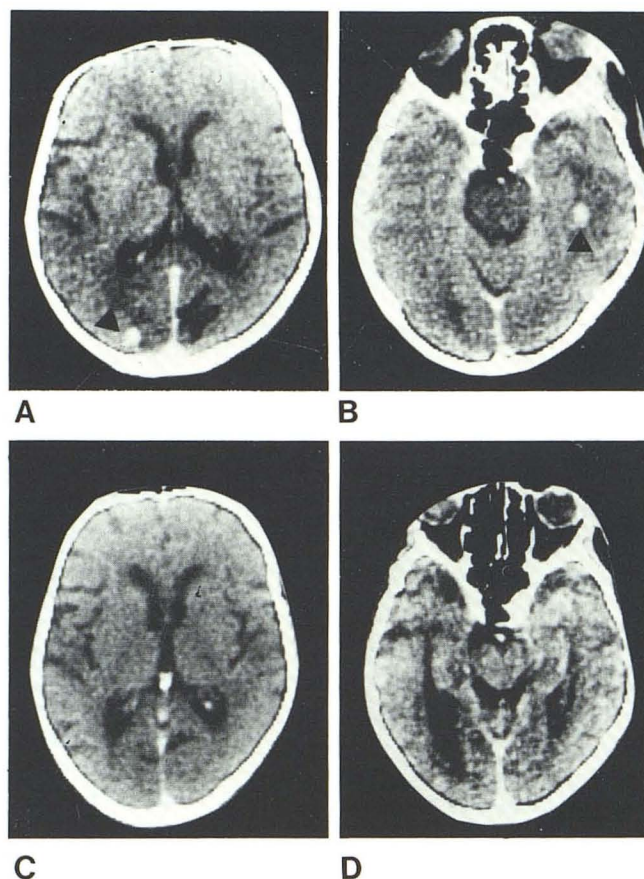


Fig. 2.—Metastatic SCC in asymptomatic patient involving left occipital (**A**) and right temporal (**B**) lobes (*arrowheads*). Follow-up CT scans demonstrate clearing of scan abnormalities at 5 (**C**) and 14 (**D**) months after completing whole brain irradiation. All scans are contrast enhanced.

basis of clinical information in eight patients.

Six group 1 patients had single sites of central nervous system (CNS) metastatic disease, most often involving either the frontal or parietal lobes, while the six patients with multiple metastases usually had disease in both cerebral hemispheres. Five group 1 patients also had evidence of SCC outside of the thorax in addition to the CNS disease

(liver, two; bone marrow, one; bone, one; and bone marrow plus bone, one) (table 2). In the other seven group 1 patients, the only metastatic disease detected was that noted on brain CT evaluation. Included within the latter seven patients was one of the neurologically asymptomatic individuals. Thus, seven of 12 group 1 patients were extensive-stage disease by virtue of intracerebral metastasis alone.

In group 2, there were 16 patients with a positive bone marrow and 20 with positive liver scans, 10 of whom also had positive marrows. Twenty-two patients had positive bone scans, eight of whom had no other site of metastatic disease (table 2).

Four group 1 patients had follow-up CT brain scans after completion of whole brain irradiation (3,000 rad [30 Gy] in 300 rad [3 Gy] fractions over 2 weeks) plus systemic chemotherapy (cyclophosphamide, adriamycin, and vincristine ± methotrexate) an average of 5.5 months after diagnosis. Three patients were undergoing routine restaging and one was being evaluated for a new lung nodule. Repeat CT scans were entirely normal in two of the patients, including the follow-up study of one of the asymptomatic patients at 5 months after diagnosis. The latter patient had a third head CT scan at 14 months after diagnosis that was also negative (fig. 2). The other two restaging CT brain scans showed progression of metastatic disease. One of the latter patients had been asymptomatic initially, and remained asymptomatic despite his worsening scan.

From a clinical perspective, there were 60 SCC patients, 39 with extensive-stage (outside thorax) and 21 with limited-stage (limited to thorax) who were neurologically asymptomatic. As noted, only two of these 60 neurologically intact individuals had a positive head CT scan. On the other hand, 24 SCC patients, 19 with extensive-stage, five with limited-stage, had abnormal neurologic evaluations at diagnosis; 10 of them had positive head CT studies. Of the other 14 patients, two had neurologic abnormalities that were clearly peripheral in origin (i.e., brachial plexus involvement). The other 12 patients had signs or symptoms suggestive of possible brain involvement (e.g., new onset headache, dementia, weakness, etc.), but no explanation was determined or the abnormality ultimately proved secondary to a metabolic derangement (e.g., IADH, hypercalcemia, ectopic ACTH) or peripheral neurologic abnormality (e.g., polyneuropathy, either due to the underlying SCC or drug-induced). Thus, 22 of 24 neurologically symptomatic patients required head CT scans to completely delineate the nature of their symptoms. Ten of 22 had a CT brain scan suggesting metastasis.

## Discussion

Staging patients with SCC currently is most useful in determining prognosis [6]. Patients with limited-stage disease survive longer than those patients with detectable disease outside the thorax [1–3]. Studies are still in progress to determine whether stage-specific therapy is warranted. If survival is improved by adding radiotherapy to the primary chest lesion in patients with limited-stage disease, the routine determination of stage will be even more important. If therapeutic cranial irradiation proves less effective than

TABLE 2: **Relation of Other Staging Procedures to CT Brain Scan Findings**

| | No. Tested | | No. Positive (%) | | p > |
|---|---|---|---|---|---|
| | + CT | – CT | + CT | – CT | |
| Chest film . . . . . . . . . . | 12 | 72 | 11 (92) | 72 (100) | 0.5 |
| Radionuclide liver scan | 12 | 68 | 2 (17) | 20 (29) | 0.1 |
| Radionuclide bone scan | 11 | 69 | 2 (18) | 22 (32) | 0.1 |
| Bone marrow aspiration/biopsy . . . . . . . | 12 | 71 | 2 (17) | 16 (23) | 0.5 |

prophylactic cranial irradiation, an area of controversy [17, 18], then establishing the presence or absence of cerebral metastases also assumes greater importance.

Central nervous system metastases in SCC patients are usually intracranial [6], although spinal cord and leptomeningeal metastases are being reported more often [4]. While asymptomatic cerebral metastases occur as documented in autopsy series [4, 19], more than 80% are recognized clinically during life [14]. Both radionuclude brain scans and CT scans are sensitive and accurate methods of detecting cerebral metastases especially in neurologically symptomatic patients [7, 13]. Although occasionally neurologically asymptomatic lung cancer patients have radionuclide brain scans suggestive of intracranial tumor, this procedure has not proved particularly useful in the routine pretreatment evaluation of the vast majority of such patients [4, 8–10]. For this reason, radionuclide brain scans should not be routinely included in the battery of pretreatment screening procedures obtained on asymptomatic patients with lung cancer [8–10].

In studies where radionuclide brain scans and CT scans have been prospectively compared, the latter appears to be more sensitive and specific for the detection of CNS metastases [11, 12, 20]. However, unlike radionuclide scans, very little is known about the value of CT brain scans in the pretreatment investigation of neurologically asymptomatic patients with lung cancer [16, 20]. This is particularly true in SCC [6, 14]. Using the head CT scan as a pretreatment screening procedure, Jacobs et al. [16] evaluated 50 neurologically intact patients with negative radionuclide scans and lung cancer clinically confined to the thorax. In this setting they found a 6% incidence of "silent" brain metastases including only one of 16 SCC patients who had an occult cerebellar metastasis detected only with the contrast-enhanced CT. Jennings et al. [21] reported a much higher incidence (21%) of clinically occult CNS lesions detected by preoperative CT brain scan in 102 neurologically asymptomatic patients with lung cancer. However, they did not define the extent of this disease in their population nor were their patients preselected on the basis of a negative radionuclide scan. Unfortunately, these authors lumped all histologic types of lung cancer together and did not specify the incidence of silent metastasis according to specific tumor histology.

Comparable with other studies [2, 3], we found a 14% incidence of CNS metastases at initial diagnosis using the head CT scan. However, unlike the findings of Jacobs et al. [16] and Jennings et al. [21], 10 of our 12 patients with positive CT scans had neurologic findings or complaints that

indicated the presence of intracerebral disease. Both asymptomatic patients with positive CT scans had multiple albeit small lesions (figs. 1 and 2) located at various sites within the brain parenchyma. One asymptomatic patient demonstrated total resolution of the CT scan abnormalities after completion of whole brain irradiation (fig. 2). Also, one symptomatic patient demonstrated normalization of the CT scan following irradiation, at which point he had become asymptomatic. In addition to radiotherapy these patients received systemic chemotherapy as previously reported [22, 23]. Although routine follow-up CT scans were not obtained on the other patients, these findings suggest that the head CT scan might be most useful in assessing tumor response to whole brain irradiation.

In a clinicopathologic evaluation of 209 SCC patients, Nugent et al. [4] found that patients with bone marrow or liver involvement at initial staging were more likely to develop CNS metastases than individuals without tumor in these sites. In our patient population, 17% with intracranial metastases at diagnosis had marrow involvement initially as compared with 22.5% without CNS disease ($p > 0.5$). Likewise, there was no difference between the two groups of patients with respect to initial liver metastases (17% versus 29%; $p > 0.1$). Nine initially asymptomatic patients eventually developed a positive CT brain scan (all of them became symptomatic, thus prompting the CT evaluation); only four of them had had either a positive bone marrow or liver scan at initial staging. Likewise, four patients who had had only a positive bone scan at diagnosis (which was *not* correlated with the subsequent development of CNS metastasis by Nugent et al. [4]) developed brain metastases. Thus, in this small group of patients, there did not appear to be a correlation between CNS metastasis at initial staging or the subsequent development of intracerebral disease and the presence of liver or marrow involvement at diagnosis.

In summary, 60 of 84 patients with SCC who underwent head CT at the time of diagnosis were neurologically asymptomatic and 58 had negative screening CT evaluations. Of the asymptomatic patients, two had CT evidence of clinically occult CNS metastases, only one of whom would have been inappropriately staged had a head CT scan not been done. Ten of our 12 patients with abnormal CT brain scans had symptoms or signs suggestive of CNS disease, and in eight the clinical findings correlated with the specific CT scan abnormality. These data do not differ from those reported by Wittes and Yeh [9], who noted a 2.8% incidence of occult lesions using the radionuclide brain scan as a screening procedure for "silent" CNS metastases in SCC. Thus, we conclude that the CT examination of the brain should not be considered part of the initial routine staging evaluation of the neurologically intact patient with SCC.

## ACKNOWLEDGMENTS

## REFERENCES

1. Greco FA, Oldham RK. Small-cell lung cancer. *N Engl J Med* **1979**;301:355–358

2. Holoye PY, Samuels ML, Lanzotti VJ, Smith T, Barkley HT. Combination chemotherapy and radiation therapy for small cell carcinoma. *JAMA* **1977**;237:1221–1224
3. Eagan RT, Maurer LH, Forcier RJ, Tulloh M. Small cell carcinoma of the lung: staging, paraneoplastic syndromes, treatment and survival. *Cancer* **1974**;33:527–532
4. Nugent JL, Bunn PA, Matthew MJ, et al. CNS metastases in small cell bronchogenic carcinoma. *Cancer* **1979**;44:1885–1893
5. Burgess RE, Burgess VF, Dibella NJ. Brain metastases in small cell carcinoma of the lung. *JAMA* **1979**;242:2084–2086
6. Ihde DC, Hansen HH. Staging procedures and prognostic factors in small cell carcinoma of the lung. In: Greco FA, Oldham RK, Bunn PA, eds. *Small cell lung cancer*. New York: Grune & Stratton, **1981**:261–283
7. Bucy PC, Ciric IS. Brain scans in diagnosis of brain tumors. *JAMA* **1965**;191:437–443
8. Hayes TP, Davis LW, Raventos A. Brain and liver scans in the evaluation of lung cancer patients. *Cancer* **1971**;27:362–363
9. Wittes RE, Yeh SDJ. Indications for liver and brain scans. Screening tests for patients with oat cell carcinoma of the lung. *JAMA* **1977**;238:506–507
10. Delaney JF, Gertz D, Shreiner DP. Usefulness of brain scans in metastatic carcinoma of the lung. *J Nucl Med* **1976**;17:406–407
11. Potts DG, Abbot GF, von Sneidern JV. National Cancer Institute study: evaluation of computed tomography in the diagnosis of intracranial neoplasms. III. Metastatic tumors. *Radiology* **1980**;136:657–664
12. Christie JH, Mori H, Go RT, Cornell SH, Schapiro RL. Computed tomography and radionuclide studies in the diagnosis of intracranial disease. *AJR* **1976**;127:171–174
13. Weisberg LA. Computerized tomography in intracranial metastases. *Arch Neurol* **1979**;36:630–634
14. Bunn PA, Nugent JL, Matthews MJ. Central nervous system metastases in small cell bronchogenic carcinoma. *Semin Oncol* **1978**;5:314–322
15. Ambrose J. Computerized x-ray scanning of the brain. *J Neurosurg* **1974**;40:679–695
16. Jacobs L, Kinkel WR, Vincent RG. "Silent" brain metastasis from lung carcinoma determined by computerized tomography. *Arch Neurol* **1977**;34:690–693
17. Cox JD, Komaki R, Byhardt RW, Kun LE. Results of whole-brain irradiation for metastases from small cell carcinoma of the lung. *Cancer Treat Rep* **1980**;64:957–961
18. Baglan RJ, Marks JE. Comparison of symptomatic and propphylactic irradiation of brain metastases from oat cell carcinoma of the lung. *Cancer* **1981**;47:41–45
19. Newman SJ, Hansen HH. Frequency, diagnosis, and treatment of brain metastases in 247 consecutive patients with bronchogenic carcinoma. *Cancer* **1974**;33:492–496
20. Deck MDF, Messina AV, Sackett JF. Computed tomography in metastatic disease of the brain. *Radiology* **1976**;119:115–120
21. Jennings EC, Aungst CW, Yatco R. Asymptomatic patients with primary carcinoma. Computer axial tomography study. *NY State J Med* **1980**;80:1096–1098
22. Greco FA, Richardson RL, Snell JD, Stroup SL, Oldham RK. Small cell lung cancer. Complete remission and improved survival. *Am J Med* **1979**;66:625–630
23. Greco FA, Hande KR, Richardson RL, Oldham RK. High dose methotrexate in combination chemotherapy for small cell lung cancer. In: Mathe G, Muggia FM, eds. *Recent results in cancer research*, vol 74. Berlin: Springer, **1980**:50–55