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Original Paper

Detection of Bone Marrow Metastases in Small Cell Lung Cancer. Comparison of Magnetic Resonance Imaging with Standard Methods

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In small cell lung cancer (SCLC), bone marrow metastases are frequently detected by bone scintigraphy (BS) and/or unilateral bone marrow biopsy and aspiration (BMBA). In this study, the value of magnetic resonance imaging (MRI) of thoracic spine and pelvis was compared with BS and BMBA and its clinical implication was evaluated in 42 patients with SCLC. Patients were staged (including BS, BMBA, CT thorax, Liver ECHO) as limited (LD) or extensive disease (ED) before and after MRI. MRI was positive in 12 BS negative ($P = 0.003$) and in 14 BMBA negative patients ($P < 0.001$), while in 8 patients, MRI was the only sign of ED, which resulted in a decrease of patients categorised with LD from 52 to 33%. However, in this small group of LD patients, there was no significant survival difference between LD (MRI pos) and LD (MRI neg) patients. It is concluded that MRI can be of value in the staging of LD patients, but it has no influence on survival.

Key words: bone marrow metastases, small cell lung cancer, magnetic resonance imaging
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INTRODUCTION

LUNG CANCER is responsible for many cancer-related deaths. Approximately 20–25% of all lung cancers are of the small cell variety [1]. Patients with small cell lung cancer (SCLC) are classified as having either limited disease (LD) or extensive disease (ED). LD is defined as a tumoral process involving only one hemithorax and its regional lymph nodes including the ipsilateral mediastinal, the ipsilateral supraclavicular and the contralateral hilar lymph nodes. All other sites of metastasis are considered ED [2]. ED is present in about 60% of newly diagnosed patients with SCLC [2]. Bone marrow (BM) involvement is a common finding in SCLC [3]. Examination of bone marrow biopsy and aspiration (BMBA) and bone scintigraphy (BS) for evidence of BM involvement are generally performed as part of the initial staging procedure. With these procedures, BM involvement at diagnosis is demonstrated in approximately 20–30% of patients [4]. However, BM involvement is seen in up to 50% in BM aspirates immunostained with monoclonal antibodies (MAb) [5–7].

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Magnetic resonance imaging (MRI) is a non-invasive imaging modality which can be used for the detection of BM involvement [8]. A few studies have been performed suggesting that MRI could detect BM metastases more frequently in SCLC [8–11]. However, these studies compared MRI with BS and BMBA immunostained with MAb [10], or they suggested only an advantage of MRI over the other modalities [8,11]. A very recent study [12] confirmed these results, but only in ED patients. The clinical relevance of these MRI findings is not yet clear.

We performed a prospective study to determine whether MRI of the thoracic spine and pelvis could detect BM metastases more frequently than BS and BMBA, procedures at present routinely performed in the staging of SCLC patients. A second aim of the study was to determine if BM metastasis detected by MRI changed the stage of the disease of the involved patients. A third aim was to assess if survival time was influenced by MRI, especially in patients who had been upstaged from LD to ED by MRI.

PATIENTS AND METHODS

From September 1991 to October 1994, 42 consecutive patients with histologically confirmed SCLC were included in

our study. There was no specific selection of patients. They ranged in age from 32 to 77 years (median 62.8 years). All patients were staged for LD or ED according to accepted conventional criteria, which included blood chemistry, liver ECHO, CT thorax, BS and BMBA. BS of the whole body was performed 3 h after injection of 15 mCi technetium 99m-HDP. BS was considered positive if lesions strongly suggestive of metastases were present.

BMBA specimens were obtained unilaterally from the posterior iliac crest. This site was not specifically associated with abnormal images in BS. Biopsies were fixed in formalin and embedded in paraffin. Histological slides were stained with haematoxylin–eosin, and the cells of the BM smears with Giemsa. After these investigations, patients were staged as LD or ED. Additionally, a MRI of thoracic spine and pelvis was performed. The MRI study was performed using a 0.5 Tesla MR imager (Gyroscan T5, Philips Medical Systems International, Best, The Netherlands). We acquired T1 weighted spin echo (SE) images of the thoracic spine (sagittal, 7 mm slice thickness, TR/TE 400/16 ms) and pelvis (transaxial, 10 mm, TR/TE 400/15 ms). Additional images with a short time inversion recovery (STIR) sequence were made of the pelvis (transaxial, 10 mm, TR/TI/TE 1400/140/22 ms). Metastasis was defined as localised areas in the BM on the SE images with a signal intensity considerably lower (Figure 1) than the surrounding bone marrow. In some patients, the marrow in virtually the whole imaged area of the axial skeleton showed a signal intensity that was considerably lower than normal fatty tissue (Figure 2). These cases were graded as diffuse metastases. In the pelvis, metastases were only diagnosed if the low intensity areas on the SE images corresponded to high intensity areas on the STIR images (Figure 3). The MRI examinations were performed by the radiologist on duty and were reviewed by one senior radiologist without knowledge of the other staging results.

All patients were initially treated with a combination chemotherapy regimen, consisting of cyclophosphamide

Figure 1. Localised dark patchy metastases (arrow) of the bone marrow on T1 weighted SE images.

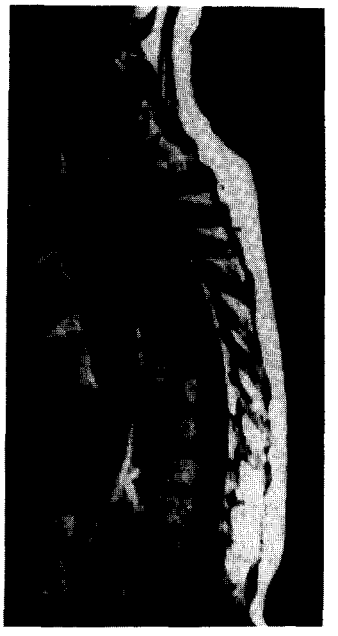

Figure 2. Diffuse metastases of the bone marrow of the axial skeleton.

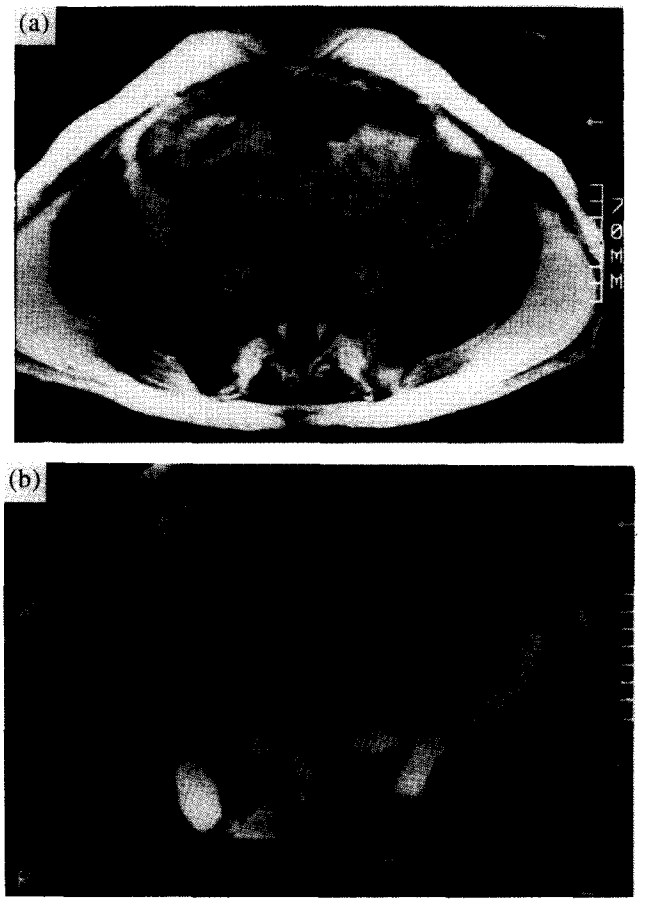

Figure 3. Pelvic metastases show low intensity areas on (a) SE images and (b) high intensity areas on STIR images.

1000 mg/m^2, doxorubicin 45 mg/m^2 and etoposide 100 mg/m^2 on days 1, 3 and 5 for at most five cycles. Chemotherapy was not followed by radiotherapy to the primary tumour site.

All patients were prospectively followed until death or until the end of the study (March 1995).

Statistical analysis of paired categorical data was undertaken using the McNemar Test. Otherwise the Chi-Square test was used. P-values < 0.05 were considered statistically significant. The statistical analyses were performed using the SPSS/for Windows Release 6.0 [13].

The survival time was calculated from the day of diagnosis till death or end of follow-up (March 1995). Kaplan–Meier survival curves were calculated and compared using the log-rank test.

RESULTS

42 patients were included in the study to evaluate the value of MRI of thoracic spine and pelvis in the initial staging procedure. In Table 1 the results are shown of the comparisons between the BM involvement found by BS, BMBA and MRI. In 12 patients, BS was negative for BM metastases, while MRI was positive for BM metastases. All positive BS were confirmed by MRI ($P = 0.003$) except for 1 patient. In this patient, BS detected a hot spot suggestive of a metastasis in the skull outside the area imaged by MRI.

BM involvement detected by BMBA was also compared with MRI. In 14 patients, BMBA was negative for BM metastases, while MRI was positive. All positive BMBAs were confirmed by MRI ($P < 0.001$), except for the patient with the positive BS in the skull who also had a positive BMBA and yet a completely normal MRI.

The result of BM involvement found by BMBA and BS together was compared with MRI. In 8 patients, BMBA as well as BS were negative, while MRI was positive. All patients with positive BS and/or positive BMBA were confirmed by MRI, with the exception of the patient mentioned above. So in 8 of these 42 patients, only MRI provided evidence for metastatic disease, which was a significant difference ($P = 0.039$).

The positive predictive value of BS or BMBA in comparison with a positive MRI was very high (93 and 92%, respectively),

Table 1. Results of magnetic resonance imaging (MRI) compared with bone scintigraphy (BS) and bone marrow biopsy and aspiration (BMBA)

	MRI		
	+	−	
BS			
+	13 (93%)*	1	
−	12 (43%)†	16	$P = 0.003$
BMBA			
+	11 (92%)*	1	
−	14 (47%)†	16	$P < 0.001$
BS and BMBA			
+	17 (94%)*	1	
−	8 (33%)†	16	$P = 0.039$

− or + are numbers of patients with a positive or negative result of examination. Values in parentheses are *positive or †negative predictive values, respectively. BS, BMBA or BS and BMBA in comparison with MRI.

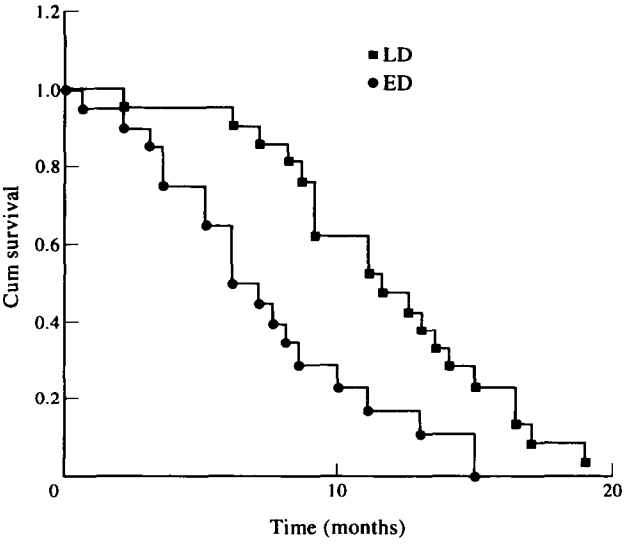

Figure 4. Kaplan–Meier survival curves of LD and ED patients. The difference between LD and ED was significant ($P = 0.0038$).

whereas the negative predictive value was low (43 and 47%, respectively), which was also true for the combination of BS and BMBA (94 and 33%, respectively) (Table 1).

According to the conventional staging (as stated in patients and methods), 22 of 42 patients had LD (52%) and 20 had ED whereas with the addition of MRI 14 of 42 (33%) had LD and 28 had ED (Chi-square: 3.11, $P = 0.08$).

The survival time of ED and LD is shown in Figure 4. The median survival time was 11.0 months (95% CI: 7.6–15.4) for LD and 6.0 months (95% CI: 3.8–8.2) for ED (logrank, $P = 0.0038$). To assess the influence of MRI on survival, the 14 patients with LD with negative MRI (median survival 12.5 months, 95% CI: 7.9–17.1) and 8 patients with LD with positive MRI (median survival 11.0 months, 95% CI: 8.3–13.7) were compared. Kaplan–Meier survival curves are shown in Figure 5. There was no significant difference in

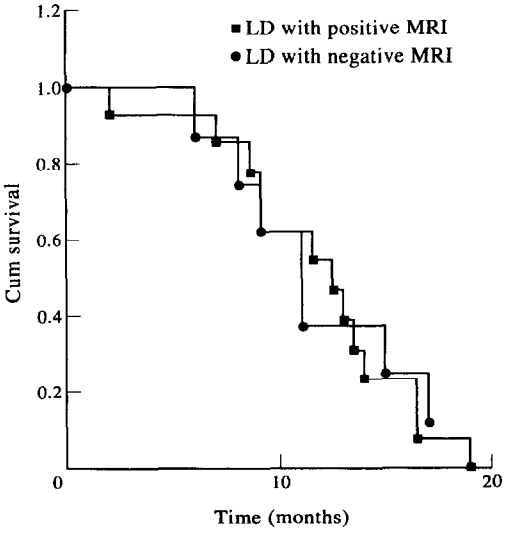

Figure 5. Kaplan–Meier survival curves of LD patients with a positive or negative MRI. There was no significant difference in survival.

survival between LD with negative MRI and LD with positive MRI.

DISCUSSION

SCLC is an aggressive neoplasm, with high risk for metastases in early disease. With current chemotherapy, patients with ED rarely remain disease-free beyond 2 years, whereas only 10–15% of patients with LD can be cured [8]. Staging procedures to detect possible sites of metastases may be necessary for certain clinical and therapeutic reasons. Firstly, it may be clinically relevant if patients with LD are treated with local and/or prophylactic cranial radiotherapy (during or after chemotherapy), in contrast to ED patients. Secondly, staging results in good prognostic indicators [3,4,10].

In patients with SCLC, BM metastases are detected in 20–30% of the patients by BS and BMBA [4, 9]. However, BM infiltration is detected in 35–66% of patients at necropsy [3, 10] and in up to 50% of BM aspirates (immunostained with MAb) [5–7]. Recently, MRI has been introduced as a procedure to detect early BM metastases [14].

Several questions have been addressed in this study. We found that MRI could enable detection of both diffuse and focal lesions when BS and BMBA were negative. BM metastases were detected in 18/42 patients (43%) by BS and BMBA while MRI detected BM metastases in 25/42 patients (60%). This shows that MRI is a more sensitive technique to detect BM metastases in SCLC than BS and BMBA. These findings have also been observed by other groups [10,11,15]. These differences in detection of BM metastases could be explained by the fact that abnormalities detected by BS reflect predominantly cortical bone involvement [10]. Although BMBA is a very specific method in detecting BM metastases, it has the disadvantage of an at random biopsy.

In addition, MRI was able to change the staging of a patient, with 8/22 LD patients changed to ED.

With our limited MRI protocol (of thoracic spine and pelvis), no metastases to ribs or appendicular skeleton were detected. However, bone metastases in SCLC outside the spine and pelvis are rare [8]. In addition, in our study, BS yielded extra information in only 1 patient (as did BMBA in the same patient). Therefore, there is probably no need to perform BS and BMBA routinely in the staging procedure when MRI is performed.

Pathological confirmation of MRI abnormalities (except for the posterior iliac crest) was not obtained as it was considered unethical to biopsy vertebrae or pelvis for research purposes only, but in some patients indirect confirmation of BM metastasis could be obtained by changes in MRI before and after chemotherapy.

There is still some doubt whether BM involvement is of prognostic significance for survival. In a small retrospective study of our institute [15], no differences were found in survival of patients with or without BM metastases. However, a prospective study of BM metastases detected by BS and BMBA showed that patients with BM metastases had a significantly shorter time to progression and a significantly shorter survival time than other patients with extensive disease [16]. Recently it was also demonstrated that patients with only BM metastases, detected by immunocytochemistry with MAb, had a worse prognosis than patients without BM infiltration and the same prognosis as patients with ED [17]. This is in contrast with the findings in our study. We only found a significant influence on survival time between LD and ED, but not between patients with LD with or without a positive MRI. Thus, MRI had no significant influence on survival time, not even in patients who has been upstaged from LD to ED. However, the patient groups were small, so the results should be interpreted cautiously.

As MRI of thoracic spine and pelvis is a time-consuming and expensive procedure, it may only be justified to apply this investigation to SCLC patients in whom extrathoracic disease has not yet been demonstrated because a positive result could change the stage of the disease in quite a number of patients. However, the findings of MRI have no significant influence on survival.

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