

## SHORT REPORT

## Brain metastases from an unknown primary tumour: which diagnostic procedures are indicated?

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### Abstract

**Seventy two patients presenting with symptomatic brain metastases from undiagnosed primary neoplasms were retrospectively reviewed. Primary malignancies were diagnosed before death in 54 patients and remained unknown in 18 patients. Lung cancer was the most common primary tumour (72%), followed by breast cancer, colon carcinoma, and melanoma. On physical examination, 51 patients had organ specific symptoms or signs providing guidelines to the diagnostic evaluation. In 24 of the 52 patients with a primary lung tumour, and in four of the 20 patients without, organ specific complaints or findings suggested this tumour type, resulting in a positive predictive value of 85%.**

**Overall, radiography and CT of the chest were very useful in detection of primary lung tumours. This could partly be explained by the high prior probability of detecting such tumours. Other diagnostic procedures should be used on indication only. The prognosis of patients with confirmed primary tumour position did not differ from those with unidentified primary tumour.**

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**Keywords:** brain metastasis; unknown primary tumour site; diagnostic evaluation

In patients presenting with brain metastases from an undetermined primary tumour site, ancillary diagnostic procedures are performed to find the underlying malignancy.

A reasonable approach to unknown primary tumours would be to avoid unnecessary diagnostic procedures, without compromising the possibility of finding the primary site, weighing the overall cost of diagnostic procedures against efficacy and clinical usefulness. The focus must be on identifying a subset of patients with neoplasms that are most amenable to successful systemic treatment, such as breast carcinoma.

In 15%–50% of patients presenting with symptomatic brain metastases, the primary tumour remains unknown, despite extensive investigations.<sup>1-3</sup>

At the Maastricht University Hospital we retrospectively studied 72 patients presenting with symptomatic brain metastases from unknown primary tumours. The aim of the present study was to evaluate this patient group to develop guidelines for further diagnostic procedures.

### Patients and methods

#### PATIENTS

All cancer patients referred for neurological consultation to the Maastricht University Hospital are registered. Methods used for case ascertainment have been described elsewhere.<sup>4</sup>

All cases coded as brain metastases from unknown primary cancers were included. Brain metastases had been diagnosed between 1987 and 1994, based on typical CT or MRI findings, with malignancy subsequently proved histologically. Metastases are depicted on CT or MRI as circumscribed contrast enhancing lesions with surrounding oedema and mass effect.

#### METHODS

Using a standard protocol, general history and physical examination data were retrospectively gathered from medical records. Information from histological examination was verified from the pathology department's database. The same procedure was followed for the radiological examinations. The radiographs were deemed abnormal if findings suggested tumour position.

The time between the first neurological consultation and the confirmation of the tumour position defines the diagnostic interval. The time from the first neurological consultation until death defines overall survival. The minimal follow up period was one year or until death.

Diagnostic intervals and survival curves were constructed using the method of Kaplan and Meier. Statistical significance was calculated by the log rank test.

### Results

Between 1987 and 1994, brain metastases from unknown primary tumours were diagnosed in 72 patients, 46 men and 26 women, with a median age of 65 (range 15–85) years.

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Table 1 Organ specific complaints and findings on history and physical examination

Localisation	History n (%)	Physical examination n (%)
Lung	26 (36)	12 (17)
Oesophagus/stomach	12 (17)	2 (3)
Colon/sigmoid	8 (11)	1 (1)
Breast	2 (3)	6 (8)
Melanoma	0 (0)	1 (1)
Kidney/urinary tract	2 (3)	3 (4)
Genitals	3 (4)	0 (0)

Brain CT was performed in 54 patients, MRI in four, and CT plus MRI in 14. Thirty eight patients had single, and 34 multiple metastases. The lesions were supratentorial in 57, infratentorial in three, and both infratentorial and supratentorial in 12.

Most of the patients (57%) had complaints suggesting an underlying malignancy. Symptoms indicating primary lung cancer were most frequent. These included altered coughing pattern, hoarseness, and dyspnoea.

Physical examination disclosed abnormalities suggesting a primary tumour in 22 patients (31%). Most of these patients had

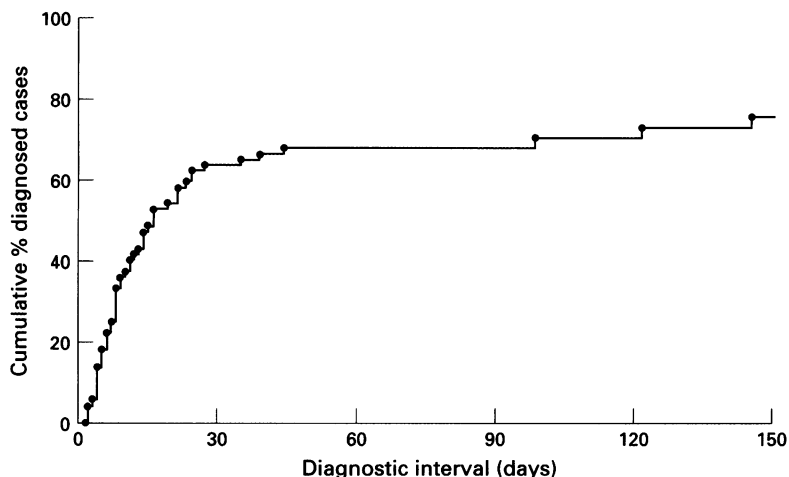


Figure 1 Diagnostic interval, time between first neurological examination and confirmation of tumour localisation. Median diagnostic interval was 15 (range 1-157) days. The curve represents the cumulative percentage of diagnosed cases.

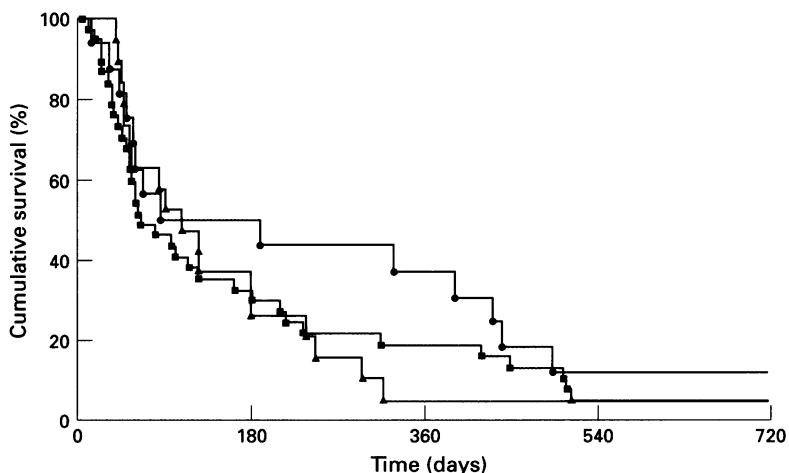


Figure 2 Survival curves of patients with a non-systemically treatable tumour (■), a systemically treatable tumour (●), and a tumour undiagnosed before death (▲). There are no significant differences between the curves (log rank 1.5 ( $P = 0.47$ )).

signs suggesting pulmonary disease. Table 1 shows data from history and physical examination ranged by primary tumour position.

Twenty four of the 52 patients who were later found to have a primary lung tumour, and four of the 20 patients without, showed symptoms or signs suggesting such a tumour. This resulted in a positive predictive value of history and physical examination of 85%.

All patients had a chest radiograph; abnormalities were detected in 56. Primary lung tumour was diagnosed in 47 patients (positive predictive value 84%).

Five patients, who later proved to have a primary lung tumour, had normal chest radiographs. In three of these, no additional diagnostic procedures were performed antemortem and the primary tumour was diagnosed at necropsy. In the two others, additional tomography or CT of the chest was performed on clinical grounds, disclosing abnormalities in both. The primary tumour was then confirmed by bronchoscopy. Tomography and CT of the chest were performed as part of the initial staging procedures in 39 patients. Mammography was performed in 13 of 26 women, disclosing abnormalities in four (31%). Breast biopsy was performed in five patients (four with abnormalities on mammography and one with a breast carcinoma stage T4, without mammography), showing abnormalities in three (60%).

The primary tumour was verified before death in 53 patients (74%). Lung cancer was the most common (48), followed by breast cancer (three), colon carcinoma (one), and melanoma (one). In five of 19 patients whose underlying malignancies were not found before death, necropsy was performed, disclosing primary tumours in four.

Malignancy was histologically confirmed within two weeks. Figure 1 shows the cumulative percentage of diagnosed cases.

Figure 2 shows the survival curves of patients with systemically treatable, non-systemically treatable, and undiagnosed tumours. The difference between the curves is not significant (log rank 1.50 ( $P = 0.47$ )), nor is the survival analysis in patients with confirmed versus unconfirmed primary tumour site (log rank 0.15 ( $P = 0.69$ )).

## Discussion

This study focused on the diagnostic approach to patients with precocious brain metastases. The primary tumour was identified before death in 53 of the 72 patients (74%) and at necropsy in four. The primary site remained unknown in 15 patients, a figure which corresponds with comparable studies, in which the underlying malignancy could not be detected in a substantial percentage of the patients, even after necropsy.<sup>1-3 5-8</sup>

Most of the patients with an identified underlying malignancy had a primary lung cancer (52 of 57). This cancer also ranked first in other studies (table 2),<sup>1-3 6-8</sup> although le Cesne *et al* found gastrointestinal tumours to be the most frequent.<sup>5</sup>

Table 2 Comparison with the literature on position of primary tumour

	Authors							
	<i>le Cesne<sup>5</sup> et al</i>	<i>Chee and Byrnes<sup>1</sup></i>	<i>le Chevalier<sup>2</sup> et al</i>	<i>Debevec<sup>6</sup></i>	<i>Dhopesh<sup>7</sup> and Yagnik</i>	<i>Hamann<sup>8</sup> et al</i>	<i>Merchut<sup>3</sup></i>	<i>Present study</i>
Year	1991	1988	1985	1990	1985	1993	1989	1995
Period	1959-80	1973-84	1959-79	1973-87	?	1975-89	1977-87	1987-93
Patients	302	51	120	75	26	122	56	72
Organ (%):								
Lung	17	41	23	53	62	48	68	72
Digestive tract	38	10	11	1	—	4	9	1
Breast	0	10	3	3	—	—	—	4
Melanoma	—	—	4	3	—	1	2	1
Urinary tract	16	8	8	1	4	5	2	0
Other	13	0	3	1	—	1	4	0
Unknown	16	31	48	37	35	42	16	21

In the Netherlands, lung cancer is the most often diagnosed primary tumour (15% of diagnosed tumours).<sup>9</sup> An estimated one third of all patients with brain metastases have a primary lung cancer.<sup>10</sup> Lung tumours thus seem to be relatively overrepresented in our patients.

In all patients with brain metastases, breast cancer is usually the second most common primary tumour.<sup>10</sup> This does not apply, however, to studies of patients with precocious brain metastases.<sup>1-3 5-8</sup> The premise of these studies is that breast cancer spreads less readily to the brain than lung cancer. Yet, breast cancer was the second most common primary tumour in our study.

Given the high frequency of primary lung tumours, the search for the primary tumour in patients with precocious brain metastases should be mainly directed towards the lung. In cases with a positive history or physical examination for primary lung tumour but a negative chest radiograph, a CT of the chest is indicated. Chest radiographs and CT proved very useful in detecting primary lung tumours, partly explained by the high percentage of these tumours. Other ancillary diagnostic procedures should be carried out if the patient's initial history or physical examination offer serious grounds for suspicion. Even with pathological confirmation of metastatic dis-

ease, identification of the primary tumour is not likely if chest radiology is negative.

In terms of duration of survival, the prognosis of patients with a confirmed primary tumour site was not better. Even patients with a systemically treatable primary tumour did not show longer survival times. Routine diagnostic protocols are unnecessarily aggravating for the patient, time consuming, and not cost effective.

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