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Site preference of metastatic tumours of the brain

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Summary. Amongst 15000 autopsies performed between 1969 and 1984 in the Department of Pathology of the University Hospital of Innsbruck (Austria) 237 cases (1.6%) with brain metastases were found. The mean age of patients was 61.2 years and 148 patients out of 230 cases with satisfactory records were male (64.3%). Multiple lesions were found in 58%. In absolute figures carcinoma of the lung, followed by malignant melanoma and breast carcinoma were, as in other series, the most frequent primary site for brain metastases. The relative frequency of brain metastases in various anatomical regions of the brain showed that malignant melanoma tends to metastasize to the frontal and temporal lobes, breast carcinoma to the cerebellum and the basal ganglia, large cell carcinoma of the lung to the occipital lobe and squamous cell carcinoma of the lung to the cerebellum. Metastases of small cell carcinoma of the lung were found equally distributed in all regions of the brain. Our study supports the results of several experimental investigations, suggesting the possibility that specific cell surface properties of metastasizing tumour cells and particular properties of the vascular endothelium of the target organs of metastasis are responsible for the location of metastases. The results of this study suggest that there are substantial differences in regard to these properties even within one target organ.

Key words: Brain neoplasms – Secondary tumours of the brain – Primary tumour dependent site preference – Metastasis

Introduction

The brain is, together with the liver and the lung, one of the predominant target organs for secondary involvement by malignant neoplasms. From most series in the literature the most frequent primary tumours causing brain metastases are carcinoma of the lung, carcinoma of the breast and malignant melanoma.

The most frequent pathway through which tumour cells or tumour emboli reach the brain is through the carotid arteries and the vertebro-basilar system (France 1975). Other comparatively rare pathways are direct invasion from adjacent tumour tissue and metastases through the vertebral venous (Batson's) plexus (Vider et al. 1977).

It is widely accepted that malignant human neoplasms show an apparent tendency to metastasize to specific secondary locations. The phenomenon of organ selectivity of metastases has often been discussed and has been the object of numerous clinical and experimental studies, which indicate that most malignant tumours tend to metastasize to particular secondary locations. There is little information in the literature concerning the tendency of metastatic tumour cells to spread to specific locations within these target organs. It was the aim of this retrospective study to analyse any site preference of brain metastases arising from different types of primary tumours. The present study was only made possible by detailed analysis and recording of brain lesions found during postmortems performed over the last fifteen years in our Department.

Materials and methods

From 1969 to 1984, among 15000 post mortem examinations performed at the Department of Pathology of the University of Innsbruck 237 adult cases (1.6%) with metastatic tumours of the brain were observed. In approximately 45% of all deaths occuring in our area (Federal State of Tyrol, Austria) postmortem examinations were performed in our Department. Paediatric cases and cases with leptomeningeal or dural involvement with absence of brain metastasis have been disregarded, as well

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as brain involvement in neoplasms of the lymphatic and the haematopoetic systems. No data for the number of hospitalized cancer patients, for tumour deaths, nor for clinical tumour distribution for the respective years were available.

The brain dissection techniques used depended whether the brain was sectioned after adequate fixation or not. Unfixed brains were examined following the method described by Komáromy (1961). Fixed brains were cut into approximately 1 cm thick slices for an exact clinico-pathological correlation of all lesions found. Detailed records of all lesions found were taken in several levels of the brain. Seven cases had to be excluded because of incomplete records. The autopsy data of the remaining 230 postmortems formed the material for the present study. Information extracted from each record: frequency, size, number and distribution pattern of brain metastases as well as histological features of the primary tumour of the respective cases.

Absolute and relative frequency of metastases in 6 anatomical regions (frontal lobe, temporal lobe, parietal lobe, occipital lobe, basal ganglia, cerebellum) were determined. The relative frequency was defined as the percentage of metastases in a certain anatomical region of all brain metastases of a certain primary tumour. The probability that the observed differences in relative frequency of metastases among different primary tumours could be due to chance was examined by the "chi-squared" test. A probability of 0.5% or less was considered as significant.

Results

The age of the patients examined ranged from 21 years to 92 years with a mean age of 61.2 years (male patients 62.8 years, female patients 59.3 years). The peak incidence of brain metastases occured in the 55–75 years age-group.

148 out of the 230 patients examined were male (64.3%), 82 were female (35.7%). The sex distribution in regard to primary tumours is shown in Table 1.

The distribution of primary tumours of the cases investigated is also shown in Table 1. They were, whenever possible, classified following the WHO-classifications of the respective organs; when necessary a reclassification was performed. Although in most cases data in regard to staging and grading of the primary tumours were available, no further subclassifications were performed for this study.

The size of metastases ranged macroscopically from 0.5 cm to 10.0 cm in diameter. No special search for micrometastases was performed.

58% of the patients had multiple lesions (2–8 lesions); a macroscopically solitary metastasis was found in 42%. The number of metastatic deposits derived from different primary tumours is shown in Table 2. Roughly equal numbers of right-sided (45.2%) and left-sided (48.9%) lesions were demonstrated, 5.9% of the metastases were located centrally.

Table 1. Distribution of primary tumours with metastases to the brain

	n	*n*%	F	–M
Lung tumours	135	58.7	30	105
Small cell carcinoma	54	23.5	6	48
Squamous cell carcinoma	29	17.6	5	24
Adenocarcinoma	25	10.9	13	12
Large cell carcinoma	25	10.9	6	19
Others	2	0.9	–	2
Malignant melanoma	22	9.6	13	9
Breast tumours	17	7.4	17	–
Gastrointestinal tract tumours	11	4.8	3	8
Oesophagus	2	0.9	–	2
Stomach	2	0.9	–	2
Colon and rectum	7	3.0	3	4
Pancreatic tumours	5	2.2	–	5
Urinary fract tumours	14	6.3	6	8
Kidney	9	3.9	4	5
Urinary bladder	4	1.7	2	2
Others	1	0.4	–	1
Testis tumours	4	1.7	–	4
Thyroid gland tumours	8	3.5	5	3
Gynecological tumours	6	2.6	6	–
Cervix uteri	3	1.3	3	–
Corpus uteri	1	0.4	1	–
Chorion carcinoma	2	0.9	2	–
Others	8	3.5	2	6
	230	100.0	82	148

n = Number of cases, *n*% = Number of cases in % (all data within the confidence limits for binominal distribution) F = Female, M = Male

Table 2. Occurence of solitary and multiple metastases in different primary tumours

	N	Solitary	Multiple
Lung tumours	135	48 (35.6%)	87 (64.4%)
Malignant melanoma	22	8 (36.4%)	14 (63.6%)
Breast tumours	17	10 (58.8%)	7 (41.2%)
Gastrointestinal tract tumours	11	8 (71.4%)	3 (28.6%)
Urinary tract tumours	14	6 (42.9%)	8 (57.1%)
Thyroid gland tumours	8	3 (37.5%)	5 (62.5%)
Others	23	12 (52.2%)	11 (47.8%)

The frequency of the occurence of metastases (single or multiple) in the various anatomical sites investigated was as follows: 24.5% of all metastases were found in the cerebellum, followed by the occipital lobe (19.9%), the frontal lobe (16.9%), the parietal lobe (9.8%), basal ganglia (9.8%) and the temporal lobe (9.0%). 4.9% of all metastases were found in other locations (including

Table 3. Absolute frequency of brain metastases in different primary tumours (in %) in various anatomical regions

	CE	OC	FR	PA	TE	BG
Lung						
Small cell carcinoma	32.7	22.8	23.1	24.4	28.6	33.3
Squamous cell carcinoma	15.9	16.3	10.3	11.1	14.3	6.7
Adenocarcinoma	9.7	9.7	7.7	13.3	9.3	11.1
Large cell carcinoma	8.9	18.5	11.5	11.1	4.8	11.1
Malignant melanoma	4.4	10.9	17.9	11.1	23.8	8.9
Breast	8.0	3.3	2.6	4.5	7.1	17.9
Gastrointestinal tract	6.1	4.3	0.0	0.0	2.4	2.2
Thyroid gland	2.7	1.1	3.9	2.2	0.0	4.4
Urinary tract	1.8	2.2	5.1	4.5	2.4	0.0
Others	9.8	10.9	17.9	17.8	7.1	4.4

CE = Cerebellum ($n = 113$), OC = Occipital lobe ($n = 92$), FR = Frontal lobe ($n = 78$), PA = Parietal lobe ($n = 45$), TE = Temporal lobe ($n = 42$), BG = Basal ganglia ($n = 45$)

the brain stem). 24 metastases (5.2%) extended to more than one anatomical region.

Seventy two point three percent of the metastases were found in the supratentorial region; in 27.7% the infratentorial region was involved.

The metastatic site predilection of each primary tumour type, expressed as a percentage of the total number of metastases found in the brain due to all types of tumours, is shown in Table 3. The more instructive information about site preference of metastases expressed within each primary tumour category is represented as a series of relative frequency histograms (Fig. 1a–f). Metastases of malignant melanomas were found preferentially in the frontal and temporal lobes (Fig. 1a, b), metastases from breast carcinoma in the basal ganglia and the cerebellum (Fig. 1e, f). The occipital lobe was the predilection site for metastases from large cell carcinoma of the lung (Fig. 1d), whereas metastases deriving from squamous cell carcinoma of the lung were found preferentially in the cerebellum (Fig. 1f). Metastases of small cell carcinoma of the lung were found almost evenly distributed in all anatomical regions of the brain.

Discussion

A number of published series have a high percentage of bronchogenic carcinomas as the cause of brain metastases with a predominance of the male sex (Simionescu 1960; Haar and Patterson 1972). Racial and environmental factors, and a different environment around reporting sites may account for some differences in the distribution of primary tumours giving rise to brain metastases. However, a substantial increase in the proportion of metastatic brain tumours of lung origin in women has been observed. This is evident in comparing recent data (Young et al. (1974): 46.3%, Schreiber et al. (1978): 59.6%, Takakura et al. (1981): 45.1%, current study: 58.7%) with earlier studies (Baker (1942): 21.1%, Stortebecker (1954): 15.8%). There is an accompanying decrease of metastases from breast carcinoma (Simionescu (1960): 22.6%, Strang and Ajmone-Marsan (1961): 29.0%, Chu and Hilaris (1961): 39.0%, Winston et al. (1980): 10.0%, Schreiber et al. (1982): 9.9%, Le Chevalier (1984): 4.8%, current study: 7.4%). These findings are due to recent advances in diagnosis and successful treatment of breast carcinoma, particularly at an early stage.

The age distribution in our study was almost the same as in other reports. The observed slight age difference between both sexes might presumably also be due to the higher incidence of lung carcinoma in men. The average age of death of patients suffering from lung carcinoma is higher than of patients with breast carcinoma and malignant tumours of the female reproductive organs (Simionescu 1960; Aronson et al. 1964; Vieth and Odon 1965). A primary tumour dependent site was demonstrated for metastases deriving from breast carcinoma (to cerebellum and basal ganglia), malignant melanoma (to frontal and temporal lobes), large cell carcinoma of the lung (to occipital lobe) and squamous cell carcinoma of the lung (to cerebellum).

There are two main hypotheses that deal with the site preference of distant metastatic deposits. Ewing (1928) thought that metastasis was influenced purely by mechanical mechanisms such as anatomical and haemodynamic factors, a theory which is now at least partly regarded as obsolete. In 1889 Paget proposed his "seed and soil" hypothesis which suggested that specific tumour cell properties and differences in the microenvironment in various organs were responsible for the nonrandom distribution of metastases. This "seed and soil" hypothesis has been supported particularly in recent years by the results of several experimental tumour studies. Using sequential in vivo selection (Fidler 1973) it was possible to obtain various tumour cell lines with common genetic origin that showed enhanced ability to colonize ovary (Brunson and Nicolson 1979), liver (Tao et al. 1979), brain (Brunson et al. 1978) and other organs. Other experiments (Fidler 1978; Irimura et al. 1981) showed that enzymatic or biosynthetic modifications of cell surface components can change

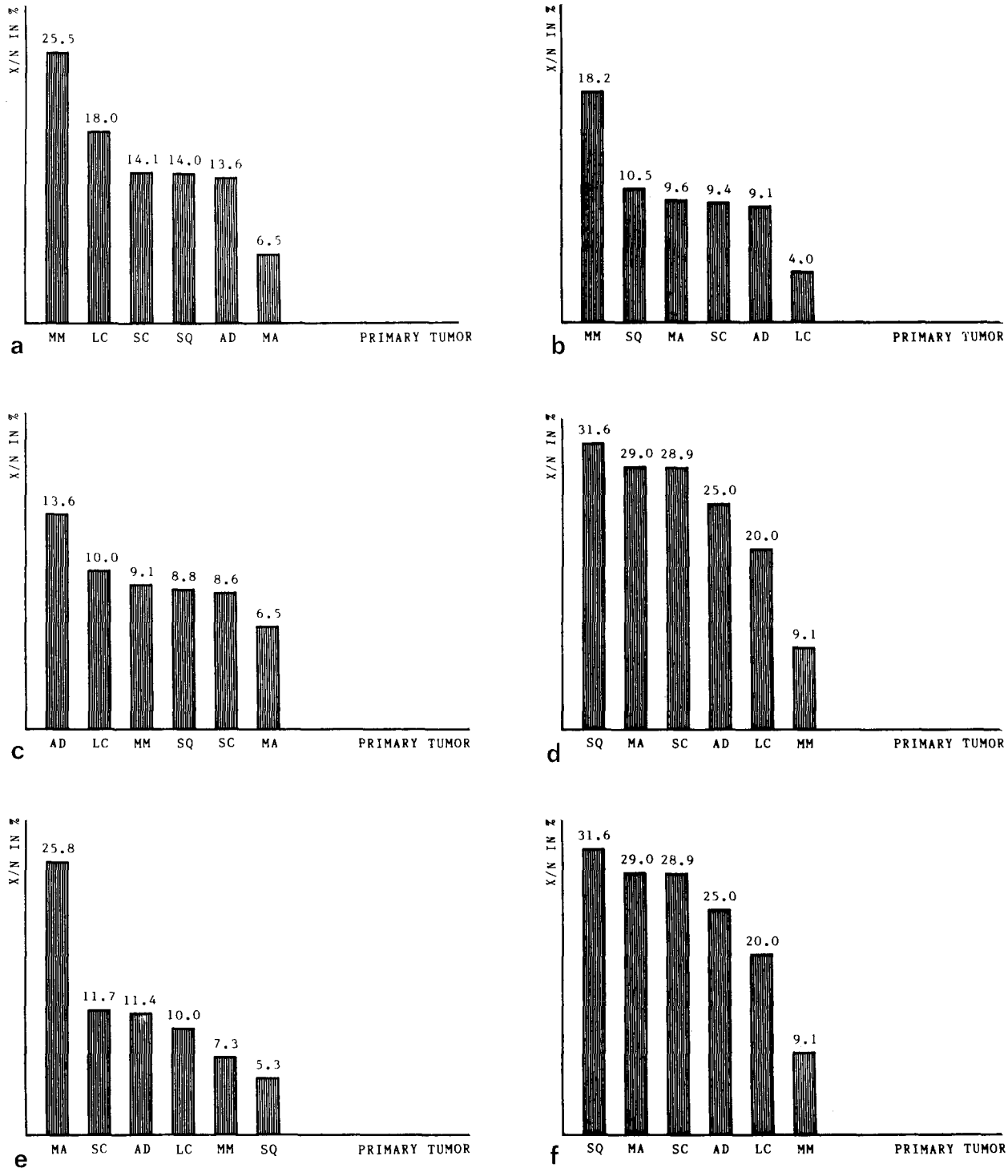

Fig. 1 a–f. Relative frequency of brain metastases (percentage of metastases in a certain anatomical region out of all brain metastases of a certain primary tumour). **a** Frontal lobe; MM/SC, MA: $p<0.05$; MM/SQ, AD: $p<0.10$; **b** Temporal lobe; MM/SC, LC: $p<0.05$; MM/AD: $p<0.10$; **c** Parietal lobe; **d** Occipital lobe; MM/SC, SQ: $p<0.01$; MM/MA, AD: $p<0.05$; **e** Basal ganglia; MM/SC, MM, SQ: $p<0.05$; MA/AD, LC: $p<0.10$; SC/SQ: $p<0.10$; **f** Cerebellum; MM/SC, SQ: $p<0.01$; MM/MA, AD: $p<0.05$. *MA* = carcinoma of the breast; *SC* = small cell carcinoma of the lung; *AD* = adenocarcinoma of the lung; *LC* = large cell carcinoma of the lung; *MM* = malignant melanoma; *SQ* = squamous cell carcinoma of the lung

implantation properties of malignant cells in the micro circulation and subsequent formation of metastases without altering tumour cell viability. Nicolson and Winkelhake (1975) studied the specific cell adhesive interactions between tumour cells and host organ in vitro. They found that B_{16} melanoma cells selected for enhanced lung colonization attached at much higher rates to lung cells than to cells from other organs. Since interactions between tumour cells and target organs of metastasis take place first at the level of the vascular endothelium, tumour cells adhesions assays were performed using vascular endothelial cell monolayers. Brain selected B_{16} melanoma cells attached at higher rates to brain derived endothelial cells when compared with endothelial cells of unrelated origin (Nicolson 1982).

There is thus strong presumptive evidence to believe that specific cell surface properties of metastasizing tumour cells on the one hand and special "receptor" abilities of the vascular endothelium of the target organs on the other are responsible for the location of metastases. As our study shows it seems that there are, even in one specific target organ, substantial differences in the distribution pattern of metastases of various primary tumours. These are possibly due to local factors in various anatomical regions, however, we are aware that the differentiation of tumours may have an important influence on the behaviour of both tumour cells and vascular endothelium.

Although there is agreement that secondary deposits of tumour cells in the cerebrum are generally multiple there have been several recently published reports dealing with the surgical treatment of brain metastases, sometimes combined with resection of the primary tumour (reviewed by Deviri et al. 1983). The main purpose of these craniotomies is often to give patients a functional home life not requiring continous nursing care (McGee 1971). In lung carcinoma in particular it is well recognised that neurological manifestations often occur when the primary tumour is still silent. It is probable that clinical suspicion of brain metastases in lung cancer is exaggerated when data from autopsy series are considered (Schmid-Wermser et al. 1974).

Further investigations may prove the clinical importance of the ability to predict metastatic behaviour of different primary tumours, particularly in regard to indistinct neurological symptoms or to the search for clinical silent brain metastases in certain primary tumours.

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