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## Clinical Manifestation and Prognostic Factors of Brain Metastases with Precocious and Metachronous Presentation

**Obraz kliniczny i rokowanie w nowotworowych przerzutach do mózgu,  
ujawniających się przed lub po rozpoznaniu ogniska pierwotnego**

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### Abstract

**Background.** Metastases are the most common type of brain tumors. They are usually revealed in patients with known malignancy (metachronous presentation), but may also become the first clinical evidence of neoplasm (precocious presentation).

**Objectives.** The aim of the study was an analysis of clinical manifestations and prognostic factors in patients with brain metastases, with special regard to those with precocious presentation.

**Material and Methods.** The study comprised 70 patients (31 women, 39 men, aged 44–77 years) with brain metastases. Retrospective analysis included: age, gender, neurological symptoms and signs, number and localization of metastases found in computed tomography (CT), primary site of neoplasm, Karnofsky Performance Status (KPS), Recursive Partitioning Analysis (RPA) classification, and method of treatment. All these parameters were compared in gender subgroups and in patients with precocious and metachronous metastases.

**Results.** The lung (42.8%) and kidney (12.9%) were the most common sources of metastases, while the primary site remained unknown in 20% of cases. The first clinical signs were motor deficits (91.4%) and increased intracranial pressure (41.4%). Epileptic seizure as the first symptom was significantly more common in men than in women. CT showed single lesions in 35.7%, multiple metastases in 61.4%, and meningeal infiltration in 2.9%. The mean KPS result was 51.1±18.3. 15.7% of patients were assigned to RPA class I, 5.7% to class II, and 78.6% to class III. 21.4% of patients were treated neurosurgically, 20% with radiotherapy, while in 58.6% only symptomatic treatment was possible. In 35.7% of cases the brain metastases were precocious and in 64.3% metachronous. Supratentorial lesions were significantly more common in cases of precocious metastases. All the patients with breast cancer had metachronous metastases. No other significant differences were found for these subgroups.

**Conclusions.** Neoplasms with CNS involvement are recognized at an advanced stage of the disease. The clinical manifestations and prognosis of precocious and metachronous brain metastases do not differ significantly (*Adv Clin Exp Med* 2007, 16, 1, 49–55).

**Key words:** brain tumors, precocious brain metastases, metachronous brain metastases.

### Streszczenie

**Wprowadzenie.** Przerzuty nowotworowe są najczęstszym typem guzów mózgu. Ujawniają się zazwyczaj u chorych z ustalonym rozpoznaniem choroby nowotworowej, mogą jednak także jej pierwszą manifestacją kliniczną.

**Cel pracy.** Analiza obrazu klinicznego i czynników rokowniczych u chorych z przerzutami do mózgu, ze szczególnym uwzględnieniem przypadków,

w których ujawnienie przerzutu poprzedzało rozpoznanie ogniska pierwotnego nowotworu.

**Materiał i metody.** Do badań włączono 70 chorych (31 kobiet, 39 mężczyzn, w wieku 44–77 lat) z rozpoznaniem przerzutów do mózgu. Retrospektywna analiza objęła: wiek, płeć, podmiotowe i przedmiotowe objawy neurologiczne, liczbę i umiejscowienie przerzutów stwierdzonych w tomografii komputerowej (TK), pierwotne umiejscowienie nowotworu, wynik w skali Karnofskiego (KPS), klasyfikację *Recursive Partitioning Analysis* (RPA), metodę leczenia. Wskaźniki te porównano dla obu płci oraz dla podgrup chorych z przerzutami rozpoznanymi przed lub po ognisku pierwotnym.

**Wyniki.** Płuco (42,8%) i nerka (12,9%) były najczęstszym pierwotnym umiejscowieniem nowotworu, a w 20% pozostało ono nieznane. Pierwsze objawy przerzutu były związane z deficytem ruchowym (91,4%) i wzmożonym ciśnieniem śródczaszkowym (41,4%). Napad padaczkowy jako pierwszy objaw był znamienne częstszy u mężczyzn niż u kobiet. U 35,7% chorych TK wykazało pojedynczy przerzut, u 61,4% – mnogie przerzuty, w 2,9% – nacieczenie opon. Średni wynik KPS wynosił  $51,1 \pm 18,3$ . 15,7% chorych zaliczono do klasy I RPA; 5,7% – II; 78,6% – III. 21,4% pacjentów poddano leczeniu neurochirurgicznemu, 20% – radioterapii, u 58,6% – możliwe było wyłącznie leczenie objawowe. W 35,7% przypadków przerzuty do mózgu ujawniły się przed, a w 64,3% – po rozpoznaniu ogniska pierwotnego. Przerzuty nadnamiotowe stwierdzono znamienne częściej w pierwszej podgrupie. U wszystkich pacjentek z nowotworem sutka, przerzuty do mózgu ujawniły się po rozpoznaniu ogniska pierwotnego. Nie stwierdzono innych znamienych różnic między podgrupami.

**Wnioski.** Nowotwory z zajęciem o.u.n. rozpoznaje się w zaawansowanym stadium choroby. Obraz kliniczny i czynniki rokownicze w przypadku przerzutów ujawniających się przed lub po rozpoznaniu ogniska pierwotnego nie wykazują istotnych różnic (*Adv Clin Exp Med* 2007, 16, 1, 49–55).

**Słowa kluczowe:** przerzuty do mózgu, rozsiany proces nowotworowy.

Metastases are the most common type of brain tumors and their frequency has increased in recent years. The central nervous system (CNS) becomes involved in 20–40% patients with neoplasm. Brain metastases are usually revealed in patients with known malignancy (metachronous presentation) or at the same time as the primary tumor (synchronous presentation). However, in 10–15% of patients, brain metastasis is the first clinical evidence of neoplasm (precocious presentation) and the primary localization of the disease often remains unknown [1, 2, 3]. Early diagnosis of the neoplasm and precise assessment of its stage is essential for an adequate choice of treatment and determining prognosis [4]. It is still a matter of debate whether the prognosis of precocious metastases is better than cases of their metachronous or synchronous presentations. How far diagnostic procedures should go in an attempt to discover the primary site of neoplasm is also under discussion [2, 5–7].

The aim of this study was an analysis of clinical manifestation and prognostic factors in patients with brain metastases, with special regard to those with precocious metastases presentation.

## Material and Methods

The study comprised 70 patients (31 women, 39 men, aged 44–77, mean: 62 years) hospitalized at the Neurological Department of Wrocław Medical University between 2002–2005 with the diagnosis of brain metastases. Retrospective analysis was performed on the basis of their medical documentation. According to case histories, the following data were defined: age, gender, symptoms and signs of CNS involvement, number and localization of metastatic lesions found in computed tomographic (CT) head scan, primary site of the neoplasm (if known), degree of disability as described by Karnofsky Performance Status

(KPS), and prognosis according to the Recursive Partitioning Analysis (RPA) classification [8]. Further choice of treatment was also noted, i.e. neurosurgery, whole brain radiotherapy (WBRT), and symptomatic pharmacological treatment. The patients were divided into two subgroups: those with precocious metastases and those with primary neoplasm already diagnosed. All the parameters defined above were compared for these subgroups. Comparison was made also for gender subgroups.

All the data were statistically analyzed. Mean and median values with standard deviations were calculated for continuous parameters and compared between the groups by one-way analysis of variance ANOVA or Wilcoxon rank test (the homogeneity of variance was determined by Bartlett's test). Frequencies of categorical parameters were assessed by the  $\chi^2$  test with the Yates correction or Fisher's two-tailed exact test (when the expected value was less than 5).  $p < 0.05$  was regarded as statistically significant.

## Results

Among the 70 patients included in the study, the lung was the primary site of neoplasm in 30 (42.8%), the kidney in 9 (12.9%), the breast in 6 (8.6%), the colon in 3 (4.3%), and the prostate in 2 (2.9%). Cancer of the uterus, throat, esophagus, and liver, skin melanoma, and lymphoma were diagnosed in a single case (1.4%) each. In 14 patients (20%) the primary site of neoplasm remained unknown. In 17 patients (24.2%), apart from brain localization, other systemic metastases were found as well: in 9 cases (12.9%) in the lungs, in 6 (8.6%) the abdomen (liver and/or retroperitoneal space), and in 2 (2.9%) in bones.

The most common early clinical signs of brain metastases (64 patients, 91.4%) were focal motor deficits (mono- or hemiparesis). In 29 patients (41.4%) symptoms and signs of increased intracra-

**Table 1.** Comparison of the analyzed parameters in gender subgroups**Tabela 1.** Porównanie analizowanych wskaźników dla obu płci

Parameter (Wskaźnik)	Women (Kobiety) (n = 31)	Men (Mężczyźni) (n = 39)	Parameter (Wskaźnik)	Women (Kobiety) (n = 31)	Men (Mężczyźni) (n = 39)	
Age – years: mean ± SD (Wiek – lata: średnia/ /odch. standard)	62.5 ± 10.9	61.6 ± 10.4	Other systemic metastases (Przerzuty o innej lokalizacji) lungs (płuca) abdomen (jama brzuszna) bones (kości)	5	4	
KPS: mean ± SD (KPS: średnia/odch. standard)	45.8 ± 20.5*	55.4 ± 17.4*		4	2	
RPA class I (RPA: klasa I)	5	6		0	2	
class II (klasa II)	0	4	Lesions shown in CT (Zmiany w TK głowy) single (pojedyncze) – right hemisphere (prawa półkula) – left hemisphere (lewa półkula) – cerebellum (mózdzek) multiple (mnogie) – supratentorial (nadnamiotowe) – supra- and infratentorial (nad- i podnamiotowe) meningeal infiltration (nacieczenie opon)	10	15	
class III (klasa III)	26	29		4	9	
Early clinical symptoms (Pierwsze objawy kliniczne) motor deficit (deficyt ruchowy) seizure (napad padaczkowy) cognitive decline (zaburzenia poznawcze) raised intracranial pressure (wzmożone ciśnienie śródczaszkowe) cerebellar syndrome (zespół mózdzkowy) oculomotor dysfunction (zaburzenia gałkoruchowe) extrapyramidal syndrome (zespół pozapiramidowy) meningeal signs (objawy oponowe) other (inne)	30	34		3	4	
	4*	17*		3	2	
	13	9		3	20	
	14	15		12	16	
	3	8		8	7	
	3	7		1	1	
	3	3		Treatment of choice (Metoda leczenia) neurosurgery (neurochirurgiczne) WBRT (radioterapia) symptomatic palliation (objawowe paliatywne)	5	10
	1	0			7	7
	3	4	19		22	
	Primary site of neoplasm (Pierwotna lokalizacja) lung (płuco) kidney (nerka) breast (sutek) prostate (prostata) colon (jelito grube) uterus (macica) throat (gardło) esophagus (przetyk) liver (wątroba) skin melanoma (czerniak – skóra) lymphoma (chłoniak) unknown (nieznana)	12	18	Presentation (Czas ujawnienia przerzutów) precocious („wczesne”) metachronous („późne”)	14	11
3		6	17		28	
6#		0#				
0		2				
1		2				
1		0				
0		1				
0		1				
0		1				
0		1				
0		1				
0		1				
8		6				

$p < 0.05$ , #  $p = 0.08$ .

\* $p < 0,05$ , #  $p = 0,08$ .

**Table 2.** Comparison of analyzed parameters in the subgroups of patients with precocious and metachronous metastases**Tabela 2.** Porównanie analizowanych wskaźników w podgrupach pacjentów z przerzutami ujawniającymi się przed („wczesne”) lub po („późne”) rozpoznaniu ogniska pierwotnego

Parameter (Wskaźnik)	Precocious metastases (Przerzuty wczesne) (n = 25)	Metachronous Metastases (Przerzuty późne) (n = 45)	Parameter (Wskaźnik)	Precocious metastases (Przerzuty wczesne) (n = 25)	Metachronous Metastases (Przerzuty późne) (n = 45)
Age – years: mean $\pm$ SD (Wiek – lata: średnia/odch. standard.)	60.4 $\pm$ 9.6	62.9 $\pm$ 11	Other systemic metastases (Przerzuty o innym umiejscowieniu)		
KPS: mean $\pm$ SD (KPS: średnia/odch. standard.)	54.8 $\pm$ 18.1	49.1 $\pm$ 19.9	lungs (płuca)	2	7
RPA class I (RPA: klasa I)	6	5	abdomen (jama brzuszna)	3	3
class II (klasa II)	1	3	bones (kości)	0	2
class III (klasa III)	18	37	Lesions shown in CT (Zmiany w TK głowy)		
Early clinical symptoms (Pierwsze objawy kliniczne)			single (pojedyncze)	7	18
motor deficit (deficyt ruchowy)	23	41	– right hemisphere (prawa półkula)	3	10
seizure (napad padaczkowy)	7	14	– left hemisphere (lewa półkula)	2	5
cognitive decline (zaburzenia poznawcze)	11	11	cerebellum (mózdzek)	2	3
raised intracranial pressure (wzmożone ciśnienie śródczaszkowe)	7	22	multiple (mnogie)	18	25
cerebellar syndrome (zespół mózdzkowy)	2	9	– supratentorial (nadnamiotowe)	15*	13*
oculomotor dysfunction (zaburzenia gałkoruchowe)	3	7	– supra- and infratentorial (nad- i podnamiotowe)	3	12
extrapyramidal syndrome (zespół pozapiramidowy)	1	5	meningeal infiltration (nacieczenie opon)	0	2
meningeal signs (objawy oponowe)	0	1	Treatment of choice (Metoda leczenia)		
other (inne)	1	6	neurosurgery (neurochirurgiczne)	8	7
Primary site of neoplasm (Pierwotne umiejscowienie)			WBRT (radioterapia)	5	9
lung (płuco)	9	21	symptomatic palliation (objawowe paliatywne)	12	29
kidney (nerka)	2	7	Gender (Płeć)		
breast (sutek)	0#	6#	women (kobiety)	14	17
prostate (prostata)	0	2	men (mężczyźni)	11	28
colon (jelito grube)	0	3			
uterus (macica)	0	1			
throat (gardło)	0	1			
esophagus (przełyk)	0	1			
liver (wątroba)	0	1			
skin melanoma (czerniak – skóra)	0	1			
lymphoma (chłoniak)	0	1			
unknown (nieznana)					

 $p < 0.05$ , #  $p = 0.08$ .\* $p < 0.05$ , #  $p = 0.08$ .

nal pressure were noted (headache, nausea/vomiting, papilledema). Twenty-two subjects (31.4%) presented with cognitive decline or deficit of higher cortical functions (disturbances of speech, memory, orientation, or behavior). In 21 patients (30%) epileptic seizure (partial or generalized) was the first symptom of brain metastasis. Among other neurological signs, cerebellar syndrome was found (ataxia of limbs or trunk, disturbed balance) in 11 patients (15.7%), oculomotor dysfunction in 10 (14.3%), palsy of other cranial nerves (no. II, V, VII, IX, and X) in 7 (10%), extrapyramidal syndrome (slowing, rigidity, tremor or other involuntary movements) in 6 (8.6%), and positive meningeal signs in 1 (1.4%).

Neuroimaging (CT head scan with iodine contrast) revealed a single metastasis in 25 patients (35.7%), these being localized in the right hemisphere in 13 cases (18.6%), in the left in 7 (10%), and in the cerebellum in 5 (7.1%). Multiple brain metastases were found in 43 patients (61.4%), these being supratentorial in 28 cases (40%) and both supra- and infratentorial in 15 (21.4%). CT showed infiltration of the meninges, resulting in hydrocephalus, in 2 patients (2.9%).

In the analyzed group, the KPS results ranged from 10–70, with a mean value of  $51.1 \pm 18.3$ . According to RPA criteria, 11 patients (15.7%) were assigned to class I, 4 (5.7%) to class II, and 55 (78.6%) to class III.

Fifteen patients (21.4%) were qualified for neurosurgical treatment, 14 (20%) for WBRT, while in the remaining 41 (58.6%) only symptomatic palliative treatment was possible. In 6 cases (8.6%) the patients died during the same stay in the hospital, several days after the brain metastases had been found.

In Tab. 1 all the analyzed data are compared according to gender subgroups. The mean result of KPS was significantly lower for women than for men (45.8 vs. 55.4). Epileptic seizure as the first clinical manifestation of metastasis was significantly more common in men than in women (17 vs. 4 cases). Differences also concerned the primary site of neoplasm: all the patients with breast cancer (the third most common localization) were female, while all with neoplasm of the throat, esophagus, and liver, skin melanoma, and lymphoma (a single case each) were male. No other statistically significant differences were found.

In 25 patients (35.7%) the brain metastases were precocious, while in 45 (64.3%) their presentation was metachronous. In Table 2 all the analyzed data are compared for these two subgroups of patients. The only statistically significant difference concerned the localization of the metastases shown in CT: supratentorial lesions were more

common in cases of precocious metastases. As for primary sites of neoplasm, all the patients with breast cancer had metachronous metastases ( $p = 0.08$ , on the edge of statistical significance). No other significant differences were found for these subgroups.

In the group of 14 patients with precocious metastases and unknown primary site of neoplasm, mean KPS was 50, but 12 were assigned to RPA class III. Single metastases were found by CT in 3 and multiple lesions in 11. The frequency of the first clinical symptoms in these patients was parallel to the whole analyzed group.

## Discussion

Knowledge of the clinical presentation of brain metastases is essential for their early recognition. In patients with known systemic cancer, even subtle signs of neurological deficit are usually suggestive of metastasis and lead to diagnostic procedures (neuroimaging). Considering a possibility of precocious presentation of metastasis, it should be suspected in any case of CNS tumor.

In the material of this study, focal motor deficit was the most common sign of brain metastases (noted in over 90%). In review papers on brain metastases, symptoms of increased intracranial pressure (especially headache) are described as prominent, with focal neurological signs noted in ca. 40% of patients [1, 3]. However, in the patients of the present study, signs of motor deficit were often subtle and found only on neurological examination, while the first subjective symptoms were indeed usually associated to raised intracranial pressure. The frequencies of seizures and cognitive decline as the first clinical manifestations of brain metastasis (ca. 30% of cases) are similar to the data reported by other authors [1, 4, 9]. It is worth mentioning that epileptic seizures occurred significantly more often in men than in women.

In 2/3 of the patients of the present study, CT revealed multiple metastases, usually supratentorial. Single metastases were more often found in the right hemisphere. In the study of Lagerwaard et al. [10], comprising 1292 patients with brain metastases, a single metastasis was found in CT in 46% of cases, with an equal frequency for both hemispheres. A similar percentage (49%) of single metastases was ascertained by Delattre et al. [11] in a smaller group of patients. Many other authors claim that contrast-enhanced MRI is more sensitive than CT in revealing the real number and size of metastases (important while considering neurosurgical treatment) [5, 9, 12]. The high percentage of patients with multiple brain metastases in the

present study, as well as the number of subjects with other systemic metastases (almost 25%), is indicative of the advanced stage of neoplasm at the moment of diagnosis. This is consistent with the results of analysis of the major prognostic factors: a relatively low mean value of KPS and poor results of RPA (more than 75% of patients in class III, with short expected survival time). In this study, a significantly lower mean KPS value was found in women, which was rather unexpected. Lagerwaard et al. [10] suggested that female sex may be a favorable prognostic factor in cases of brain metastases, but only from lung primary malignancy. Other authors do not show any relationship between sex and prognosis in brain metastases [1, 4, 9].

Knowledge of the most frequent sources of brain metastases allows an adequate choice of further diagnostic procedures and treatment options. Lung cancer (especially adenocarcinoma) is commonly regarded as the most frequent site of primary malignancy, no matter when the brain metastases were revealed. In the material of the present study a similar result was observed, with ca. 40% cases of lung cancer. Among the other localizations of primary neoplasm in this study there were more cases of kidney and colon cancer than in the cited studies, but only one case of melanoma, regarded as one of the commonest sources of metastases [1, 13]. It is worth mentioning that in all the cases of breast cancer, the presentation of brain metastases was metachronous. Merchut et al. [14] and Kirsch et al. [15] confirmed such a relationship and associated it to the natural course of breast cancer, with late involvement of the CNS.

In the present study, the patients with precocious presentation of brain metastases made up 35.7% of the whole analyzed group, which is also indicative of late recognition of neoplasm in the population. In more than half of these the source of metastases remained unknown, in spite of a basic diagnostic investigation. According to many authors, primary neoplasm remains unrecognized in 15–50% of cases despite thorough investigation (in 1.6–3% even at autopsy) [2, 7, 16].

The clinical manifestations of brain metastases with precocious and metachronous presentation did not differ in general. The only significant finding concerned localization of lesions shown in CT: supratentorial metastases (with no involvement of the posterior fossa) were more common in precocious metastases. A more common occurrence of supratentorial metastases is usually attributed to

relatively greater mass and blood flow of supratentorial brain structures. Infratentorial localization of metastases, in turn, is observed as typical of pelvic and abdominal primary tumors [1, 11, 13]. However, such localization of the primary neoplasm was similar for precocious and metachronous metastases, so the reasons for the ascertained difference in neuroimaging findings remain unclear.

In the present study, the major prognostic factors (KPS and RPA classification) did not differ significantly between the subgroups with precocious and metachronous presentation. Nguyen et al. [16] suggested on the basis of serial CT results that the prognosis for precocious metastases is better than for brain metastases in general. Apart from this study, it is generally claimed that a precocious presentation of brain metastases, as well as detection of the primary malignancy, does not affect prognosis significantly, apart from cases of cancer amenable to specific systemic treatment (e.g. breast cancer) [2, 5, 7, 14]. In view of this, it is often a matter of debate how far a systemic investigation should be pursued in an attempt to find the primary site of a neoplasm. It seems reasonable to perform a basic systemic investigation directed towards the commonest sources of brain metastases. When the primary site of the neoplasm remains unknown, further procedures (especially invasive ones) should be considered only in view of the patient's expected survival time and quality of life [5,14]. As only a few patients may benefit from intensive treatment of primary neoplasm, adequate palliative treatment is essential at this stage of the disease [17].

## Conclusions

Neoplasms with CNS involvement are recognized at an advanced stage of the disease, with unfavorable prognosis and few therapeutic options. The first clinical symptoms of brain metastases are connected with motor deficit and/or raised intracranial pressure. The most common sources of brain metastases are the lung, kidney (in men), and breast (in women). In a substantial portion of cases of precocious brain metastases, the primary site of neoplasm remains unknown. The clinical manifestations and prognosis of precocious and metachronous brain metastases do not differ significantly.

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