Research Article

Characteristics of Brain Tumor Metastases at dr. Cipto Mangunkusumo National Referral Hospital

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Abstract

Metastatic brain tumors, surpassing primary brain tumors in prevalence by tenfold, are the most common brain neoplasms, emphasizing the role of early diagnosis in improving the patient's quality of life. This study aimed to identify the characteristics of brain tumor metastases at dr. Cipto Mangunkusumo National Referral Hospital (RSCM). With consecutive sampling, a cross-sectional design study using secondary brain tumor data was conducted at RSCM from January 2016 to December 2020. Characteristics data were presented in percentages, and bivariate analysis was conducted using Chi-square or Fisher's test. Among 222 subjects (mean age 50.9 ± 10.4 years, 60.8% women), metastases were predominantly supratentorial (50.6%), multiple (65.8%), and associated with mass effects (51.4%), particularly midline shift (69.6%). Primary tumors were predominantly lung (36.5%), breast (34.2%), and 55.9% experienced metastases in other organs. Brain metastases manifested metachronously in 67.6% of cases, with primary breast tumors showing a higher propensity for metatentorial and infratentorial metastases, while primary lung tumors showed a synchronous onset. The study highlighted associations between mass effects, loss of consciousness, and poor performance in subjects. Primary lung and breast tumors exhibited the highest incidence of brain metastases.
Keywords*: brain tumor, characteristic, metastatic.*

Karakteristik Tumor Otak Metastasis di RS Rujukan Nasional dr. Cipto Mangunkusumo

Abstrak

Tumor otak metastatik, yang prevalensinya melebihi tumor otak primer sebanyak sepuluh kali lipat, merupakan neoplasma otak yang paling umum, sehingga menekankan peran diagnosis dini dalam meningkatkan kualitas hidup pasien. Penelitian ini bertujuan untuk mengetahui karakteristik metastasis tumor otak di RSCM. Dengan metode consecutive sampling, sebuah studi desain cross-sectional menggunakan data tumor otak sekunder dilakukan di RSCM sebagai Rumah Sakit Rujukan Nasional dari Januari 2016 hingga Desember 2020. Data karakteristik disajikan dalam persentase, dan analisis bivariat dilakukan dengan menggunakan uji Chi-square atau Fisher. Di antara 222 subjek (usia rata-rata 50,9 ± 10,4 tahun, 60,8% perempuan), metastasis dominan terjadi di supratentorial (50,6%), multipel (65,8%), dan berhubungan dengan efek massa, terutama pergeseran garis tengah (69,6%). Tumor primer terbanyak adalah paru (36,5%) payudara (34,2%), dan 55,9% mengalami metastasis ke organ lain. Metastasis otak bermanifestasi secara metachronous pada 67,6% kasus, dengan tumor payudara primer menunjukkan kecenderungan lebih tinggi untuk bermetastasis metatentorial dan infratentorial, sedangkan tumor paru primer menunjukkan onset yang sinkron. Studi ini menyoroti hubungan antara efek massa, penurunan kesadaran, dan kinerja buruk pada subjek. Tumor primer paru-paru dan payudara merupakan insiden metastasis otak tertinggi.
Kata kunci*: tumor otak, karakteristik, metastasis.*

Introduction

Metastatic brain tumors, occurring ten times more frequently than primary cases, represent a major category of brain neoplasms, with over 70,000 new cases reported annually in 2016. This prevalence underscores their notable impact on public health, as over 40% of systemic tumors exhibit a propensity for brain metastasis, leading to symptomatic presentations in 60-75% of cases.[1-3] Early detection becomes imperative, given that a considerable portion of these tumors is incidentally discovered during imaging or autopsy.

Differentiating metastatic from primary brain tumors is crucial, guiding distinct diagnostic and treatment approaches. Primary brain tumors often necessitate direct surgery for histopathological diagnosis, while the complexity of managing metastatic brain tumors requires an intricate diagnostic journey, especially when the primary tumor remains unidentified. Diagnostic tools, including imaging and tumor markers, are pivotal in locating primary organs and potential metastases.[4]

The absence of routine screening for solid primary tumors without neurological deficits underscores the need to explore the characteristics of metastatic brain tumors. Despite the critical implications for patient care and treatment strategies, Despite the critical implications for patient care and treatment strategies, detailed research on clinical characteristics and diagnostic approaches remains limited in Indonesia. This study aims to provide comprehensive insights into the characteristics of metastatic brain tumors, offering valuable reference points for rapid diagnosis and serving as foundational knowledge for neurologists and patient education.

Methods

This study employed a cross-sectional descriptive design with an analytical approach, using secondary data from medical records focused on patients diagnosed with metastatic brain tumors at RSCM Jakarta from January 2016 to December 2020. Inclusion criteria encompassed individuals aged >18 years with confirmed diagnoses of metastatic brain tumors supported by satisfactory histopathological results. Exclusions involved patients with incomplete records, blood cancer, and head and neck area cancers infiltrating the intracranial region. Data on demographic, clinical, and tumor characteristics were presented using frequencies and percentages. The relationship between categorical variables was assessed using the chi-square or Fisher's exact test with SPSS version 20.

This research obtained approvals from the Universitas Indonesia's Research Ethics Committee (No. KET-80/UN2.F1/ETIK/PPM.00.02/2021) and RSCM (No. LB.02.01/2.6.1/0360/2021). Strict confidentiality measures were maintained for subjects' identities and examination results.

Results

Demographic and Clinical Characteristics of Subjects

A total of 222 individuals were included in this study. The majority of subjects were women (60.8%), with a mean age of 50.9 ± 10.4 years, an education level exceeding level 9 (85.6%), and a marital status of married (82%). Only 17.1% of subjects were smokers (Table 1).

Table 1. Demographic Characteristics (n=222)

Characteristics	n (%)
Gender	
Male	87 (39.2)
Female	135 (60.8)
Age (years)	
<50 years old	97 (43.7)
>50 years old	125 (56.3)
Education	
<9 years	32 (14.4)
>9 years	190 (85.6)
Marital Status	
Married	182 (82.0)
Unmarried	40 (18.0)
Working Status	
Yes	104 (46.8)
No	118 (53.2)
Smoking	
Yes	38 (17.1)
No	184 (82.9)

Tumor Characteristics in Subjects

Metastatic brain tumors, predominantly situated in the supratentorial area (50.5%) with multiple lesions (65.8%), often present mass effects in 51.4% of cases, including midline shift (69.6%), hydrocephalus (23.7%), and ventricular narrowing (16.7%). Primary tumors commonly linked to metastasis include lung (36.5%), breast (34.2%), and gynecological tumors (9%), with 55.9% of subjects concurrently diagnosed with metastases to other organs, notably lung (52.4%), bone (51.6%), and liver (27.4%). Adenocarcinoma was the predominant anatomical pathology observed, contributing to 38.7% of cases. Analyzing the transition of primary tumors into brain metastases, 67.6% of subjects exhibited metachronous symptoms, indicating that the symptoms of brain metastases were identified after recognizing the primary tumor. Synchronous or simultaneous onset occurred in 21.2% of cases, while 11.3% displayed a precocious or delayed symptom manifestation (Table 2 and Table 3).

Table 2. Clinical Characteristics

Clinical Characteristics	n (%)
Headache	
Yes	142 (64)
No	80 (36)
Headache onset (n=142)	
Acute	60 (42.3)
Chronic-progressive	82 (57.7)
Headache intensity (n=142)	
Mild	10 (7)
Moderate	52 (36.6)
Severe	80 (56.3)
Headache location (n=142)	
Focal	52 (36.6)
Diffuse	90 (63.4)
Headache characteristics (n=142)	
Tension-type headache-like	45 (31.7)
Migraine type-like	27 (19)
Atypical	70 (49.3)
With Vomiting (n=142)	
Yes	47 (33.1)
No	95 (66.9)
Seizure	
Yes	61 (27.5)
Generalized	8(13.1)
Focal	53(86.9)
No	161 (72.5)
Motoric disturbance (n=222)	
Yes	151 (68)
No	71 (32)
Sensory disturbance (n=150)	
Yes	11 (7.4)
No	139 (92.6)
Visual disturbance (n=222)	
Yes	66 (29.7)
No	156 (70.3)
Ataxia (n=222)	
Yes	14 (6.3)
No	208 (93.7)
Vertigo (n=222)	
Yes	20 (9)
No	202 (91)
Cognitive Impairment (n=36)	
Yes	24 (66.7)
No	12 (33.3)
Loss of consciousness (n=222)	
Yes	71 (32)
Mild (GCS ≥13)	22 (31.9)
Moderate (GCS 9-12)	41(59.4)
Severe (GCS ≤8)	6 (8.7)
No	152 (68.5)
Karnofsky Performance Status/KPS (n=222)	
Good (≥ 60)	115 (51.8)
Poor (<60)	106 (48.2)
Cancer pain (n=222)	
Yes	82 (36.9)
No	140 (63.1)
Hypercoagulation (n=221)	
Yes	128 (57.7)
No	94 (42.3)

Table 3. Tumor Characteristics

Tumor Characteristics	n (%)
Lesion location (n=222)	
Supratentorial	112 (50.5)
Infratentorial	14 (6.3)
Supratentorial and Infratentorial	96 (43.2)
Leptomeningeal	19 (8.6)
Number of Lesions (n=222)	
Single	76 (34.2)
Multiple	146 (65.8)
Mass effect (n=222)	
Yes	114 (51.4)
No	108 (48.6)
Midline shift (n=114)	
Yes	80 (69.6)
No	34 (30.4%)
Ventricular narrowing (n=114)	
Yes	19 (16.7)
No	95 (83.3)
Hydrocephalus (n=114)	
Yes	28 (23.7)
No	86 (76.3)
Types of primary tumor (n=222)	
Lung	81 (36.5)
Breast	76 (34.2)
Melanoma	10 (4.5)
Colorectal	8 (3.6)
Renal	8 (3.6)
Gynecology	20 (9.0)
Others	18 (8.1)
Pathology (n=222)	
Adenocarcinoma	86 (38.7)
Invasive ductal carcinoma	55 (24.8)
Squamous cell carcinoma	28 (12.6)
Others	53 (23.9)
Distant metastases (n=222)	
Yes	124 (55.9)
Lung	65 (52.4)
Liver	34 (27.4)
Bone	64 (51.6)
Others	8 (6.5)
No	98 (44.1)
The onset of primary tumor to brain metastases (n=222)	
Metachronous	150 (67.6)
Synchronous	47 (21.2)
Precocious	25 (11.3)

Relationship between Primary Tumor Type and Location of Metastases and The Onset of Primary Tumors Becoming Brain Metastases

Table 4 showed a simultaneous metastasis of the primary breast tumor type to both supratentorial and infratentorial regions (p=0.045). Furthermore, all primary renal tumors exclusively metastasized to the supratentorial area (p=0.015).

Table 4. Relationship between Primary Tumor Type and Location of Metastases (n=222)

Types of Primary Tumor	Supratentoria n (%)	Infratentorial n (%)	Both n (%)	p
Lung				
Yes	36 (44.4)	10 (12.3)	35 (43.2)	0.288
No	74 (52.5)	21 (14.9)	46 (32.6)	
Breast				
Yes	29 (38.2)	14 (18.4)	33 (43.4)	0.045*
No	81 (55.5)	17 (11.6)	48 (32.9)	
Melanoma				
Yes	3 (30)	0	7 (70)	0.291
No	103 (48.6)	31 (14.6)	78 (36.8)	
Colorectal				
Yes	4 (50)	2 (25)	2 (25)	0.599
No	106 (49.5)	29 (13.6)	79 (36.9)	
Renal				
Yes	8 (100)	0	0	0.015*
No	102 (47.7)	31 (14.5)	81 (37.9)	
Gynecology				
Yes	13 (65)	2 (10.0)	5 (25)	0.350
No	97 (48)	29(14.4)	76 (37.6)	
Others				
Yes	12 (66.7)	3 (16.7)	3 (16.7)	0.185
No	98 (48)	28(13.7)	78 (38.2)	

Table 5 shows the pattern of brain metastasis onset concerning primary carcinoma, encompassing metachronous, synchronous, and precocious instances. The analysis revealed a significant metachronous onset among subjects with breast and gynecological malignancies (p=<0.001 and p=0.005, respectively). Conversely, lung malignancies tend to have a synchronous onset (p<0.001).

Table 5. The Association between The Primary Tumor Type and The Primary Tumor Timing Evolving into Brain Metastases (n=222)

Primary Tumor Type	Metachronous n (%)	Synchronous n (%)	Precocious n (%)	p
Lung				
Yes	20 (24.7)	38 (46.9)	23 (28.4)	<0.001*
No	130 (92.2)	9 (6.4)	2 (1.4)	
Breast				
Yes	74 (97.4)	2 (2.6)	0	<0.001*
No	76 (52.1)	45 (30.8)	25 (17.1)	
Melanoma				
Yes	10 (100)	0	0	0.081
No	140 (66.0)	47 (22.2)	25 (11.8)	
Colorectal				
Yes	5 (62.5)	2 (25)	1 (12.5)	0.951
No	145 (67.8)	45 (21.0)	24 (11.2)	
Renal				
Yes	6 (75)	2 (25)	0	0.589
No	144 (67.3)	45 (21.0)	25 (11.7)	
Gynecology				
Yes	20 (100)	0	0	0.005*
No	130 (64.4	47 (23.3)	25 (12.3)	
Others				
Yes	14 (77.8)	3 (16.7)	1 (5.5)	0.599
No	136 (66.7)	44(21.6)	24 (11.7)	

The Correlation between Mass Effects, Metastases in Other Organs, and Clinical Manifestations with The Performance Score

Table 6 illustrates a correlation between the mass effect and poor subject performance (KPS <60), denoted by p<0.001. Contrarily, Table 7 clarifies that metastases from other organs did not significantly impact the subject's performance in this study. Table 5 also presents that decreased consciousness was linked to poor subject performance (p=<0.001).

Table 6. The Correlation between Mass Effects, Metastases in Other Organs, and Clinical Manifestations with The Performance Score

Variable	Performance Score		p
	Good (KPS ≥60) n (%)	Poor (KPS <60) n (%)	
Mass Effect			
Yes	28 (24.6)	86 (75.4)	<0.001*
No	87 (81)	21 (19)	
Midline shift			
Yes	22 (27.5)	58 (72.5)	0.394
No	7 (20)	28 (80)	
Ventricle narrowing			
Yes	3 (15.8)	16 (84.2)	0.331
No	25 (26.3)	70 (73.7)	
Hydrocephalus			
Yes	5 (20)	21 (80)	0.472
No	23 (26.1)	65 (73.9)	

**chi-square*

Table 7. The Association between The Presence of Metastases in Other Organsand Clinical Manifestations with the Performance Score

Variable	Performance Score		p
	Good (KPS ≥60) n (%)	Poor (KPS <60) n (%)	
Metastases to other organ			
Distant metastases			
Yes	67 (54.9)	55 (45.1)	0.305
No	48 (48)	52 (52)	
Lung metastases			
Yes	39 (60)	26 (40)	0.225
No	29 (49.1)	30 (50.9)	
Liver metastases			
Yes	17 (50)	17 (50)	0.506
No	51(56.7)	39 (43.3)	
Bone metastases			
Yes	33 (54.1)	31 (45.9)	0.449
No	35 (58.3)	25 (41.7)	
Clinical manifestations			
Decrease of consciousness			
Yes	18 (25.4)	53 (74.6)	<0.001*
No	97 (64.2)	54 (35.8)	
Headache			
Yes	73 (51.4)	69 (48.6)	0.876
No	42 (52.5)	38 (47.5)	
Cancer pain			
Yes	40 (48.8)	42 (51.2)	0.491
No	75 (53.6)	65 (46.4)	
Seizure			
Yes	35 (58.3)	25 (41.7)	0.253
No	81 (50)	81 (50)	

**chi-square*

Discussion

Subject Demographic Characteristics

In this study, breast cancer accounted for 34.2% of cases and predominantly affected female patients, who made up 60.8% of the cohort, reflecting the prevalence of breast cancer as a primary tumor. The mean age of subjects with metastatic brain tumors was 50.9±10.4 years, with a majority falling into the >50 years age group (56.3%). This contrasts with Barnholtz et al[5] research that reported the highest median age for metastatic brain tumors as 59 years, and SEER data indicating the peak proportion at 60 years.[3,5] The variance may stem from the earlier onset of breast cancer in Indonesia (40-49 years).[6] Most subjects had a standard Indonesian education exceeding level 9 (85.6%) and were married (82%). However, while lung cancer was the most common primary tumor (36.5%) and linked to smoking (17.1% of subjects), the study does not explicitly provide a gender-specific breakdown for lung cancer cases. Soemantri et al[7], revealed that active smoking, linked to a 13-fold increase in lung cancer risk, was evident in 75% of lung cancers metastasizing to the brain.[7,8]

Clinical Characteristics of Subjects

Subjects in this study commonly presented with motor disorder (68%) and headaches (64%), consistent with Noh et al[9] findings of focal deficits as predominant neurological manifestations in metastatic brain tumors (20−75%), accompanied by headaches (25−57%).[9] These patterns resulted from the mass effect of tumor mass and perifocal edema. The onset correlated with mass effects and multiple metastases indicative of slow, progressive, and diffuse headaches linked to increased intracranial pressure (ICP). Red flag signs for secondary headaches included chronic, progressive nature and the presence of papilledema.[10] Cognitive impairment affected 65.7% of subjects, consistent with Chang et al[11] findings in metastatic brain tumor patients (67%). The study indicates micro infiltrative tumor growth and diaschisis processes influencing cognitive impairment, deviating from Maharani et al[14] RSCM study (85%), possibly due to the specific examination of high-functioning brain tumor patients.[12-14]

Decreased consciousness was observed in 32% of subjects, mainly presented as a moderate decrease (GCS 9-12), suggesting severe neurological deficit upon hospital admission, corroborated by 48.2% exhibiting poor performance (KPS <60). Seizures occurred in 27.5% of subjects, predominantly as focal seizures (86.9%), aligning with Noh et al[9] observation of lower seizure tendency in metastatic brain tumors compared to primary tumors (24%), and the risk may increase with multiple lesions.[2,8,14] Cancer pain (36.9%) was prominent, particularly in those with bone metastases, surpassing Tanjung et al[16] RSCM study (29.9%).[16] Zhu et al[17] emphasized the impact of bone metastasis-related pain on patients' quality of life, attributing it to tumor growth factor secretion and altered pH levels.[16] Hypercoagulation affected 57.7% of subjects, resembling Tunjungsari et al[18] RSCM findings (47.4%), with malignancy-induced hypercoagulability.[17] Lima et al[19] highlighted blood coagulation cascade activation in the tumor microenvironment, consistent with Suega et al[20] emphasis on elevated D-dimer levels as markers of advanced malignancy stages.

Tumor Characteristics

Metastases in this study predominantly occurred in the supratentorial area (50.6%) with multiple lesions (65.8%), deviating from the general literature that suggests 80% in cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem.[1,2,21] This variance may stem from hematogenous spread, favoring the watershed area of the brain and consistent with the micro emboli origin, hence the supratentorial predominance.[1,2,20] Mass effects were prevalent in 51.4% of subjects, manifesting as midline shift (69.6%), hydrocephalus (23.7%), and ventricular narrowing (16.7%). Most presented with ICP, notably highlighted by midline shift as a crucial marker indicating elevated intracranial pressure and reduced cerebral perfusion due to mass effect.[22]

Primary tumors were most commonly lung (36.5%), breast (34.2%), and gynecological (9%), aligned with another study.[23] Adenocarcinoma (38.7%) dominated anatomical pathology, consistent with poor prognosis and high recurrence rates observed in the literature.[24-26] Lung cancer, particularly adenocarcinoma, is well-documented as a frequent brain metastasis origin.[27] Among subjects, 55.9% experienced metastases in other organs when brain metastases were diagnosed, notably in the lungs (52.4%) and bones (51.6%). This migration pattern underscores the hematogenous route, with the lungs serving as a prominent site before metastasizing to the brain. Lung and bone metastases are common.[28-30]

Regarding onset, 67.6% experienced metachronous symptoms, 21.2% synchronous, and 11.3% precocious. These findings mirror previous research, such as Shibahara et al[31] retrospective study, which reported 64% metachronous cases. This aligned with the natural progression where

clinical manifestations appear first in the organ of origin, preceding vascular invasion and subsequent metastasis, revealing symptoms in the metastatic organ.

Primary Tumor Type, Onset of Brain Metastases, and Location Relationship

Examining the onset of brain metastases concerning primary carcinoma types, subjects with breast and gynecological malignancies significantly experienced metachronous onset. Breast cancer, requiring an average of 44 months to metastasize to the brain, often manifests symptoms in the organ of origin first, followed by metastases.[24] Similarly, gynecological malignancies commonly exhibit metachronous onset, with an average metastasis time of 25.4 months.[26,31]

Contrastingly, lung malignancies tended to show synchronous onset. The proximity of the lung stothebrain's blood flow contributes to the manifestation of symptoms in the brain before the organ of origin. Difficulty detecting primary lung tumors underscores the importance of chest CT scans for early identification.[31] Additionally, the primary breast tumor type demonstrated the ability to metastasize both supratentorial and infratentorial simultaneously (p=0.045). Breast malignancies, especially HER2-positive and ER-negative subtypes, showed higher metastases in infratentorial.[32] In contrast, primary renal tumors consistently metastasized to the supratentorial area (p=0.015), aligned with the tendency of renal malignancies to favor supratentorial metastases (70%).[33]

The tendency of HER2-positive and ER-negative breast cancer subtypes to metastasize more frequently to the infratentorial region suggests unique molecular or vascular characteristics facilitating metastasis to this area. Similarly, the consistent localization of renal tumor metastases in the supratentorial region may reflect differences in metastatic pathways or microenvironmental compatibility. These insights underline the importance of tailoring imaging and surveillance strategies based on the primary tumor's subtype and typical metastatic patterns, which can improve early detection and targeted intervention.

Mass Effect, Metastases, and Clinical Manifestations Impact on Performance Score

The study revealed a significant association between mass effects and poor performance scores. Intracranial tumors causing mass effects result in neurological deficits, including headaches, decreased consciousness, visual disturbances, or seizures.[34] The prevalence of multiple lesions and ICP contributed to the observed poor performance in subjects.

This study's limitations include its cross-sectional design, single-center setting, and reliance on retrospective data, which may affect the generalizability and depth of findings. Future research should consider multi-center collaborations, longitudinal designs, and the inclusion of molecular profiling to explore the mechanisms of metastasis and improve diagnostic and therapeutic strategies.

Conclusion

This study revealed that primary tumors in patients with metastatic brain tumors most commonly originated from the lung (36.5%) and breast (34.2%). Among these patients, 55.9% presented with metastases to other organs, with the lungs (52.4%) and bones (51.6%) being the most frequent sites. Brain metastasis symptoms manifested metachronously in 67.6% of cases, notably with primary breast tumors demonstrating both supratentorial and infratentorial metastases. In contrast, most primary lung tumors exhibited synchronous onset. The study emphasizes the correlation between mass effects, diminished awareness, and impaired subject performance.

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