

Ct Scan And Mri Appearance Of Brain Metastasis In Lung Adenocarcinoma Patients With Epidermal Growth Factor Receptor Mutation Status Evaluation In Dr. Soetomo General Hospital

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Timban J.F.J^a, Erawati D^b, Soeprijanto B^b, Widyoningroem A^b

^a joanfebry3@gmail.com

^aResident, Department of Radiology, Faculty of Medicine Airlangga University, Dr. Soetomo General Academic Hospital Surabaya, Indonesia

^bRadiologist, Department of Radiology, Faculty of Medicine Airlangga University, Dr. Soetomo General Academic Hospital Surabaya, Indonesia

Abstract

This study aims to find the prevalence and appearance of brain metastasis from CT and MRI in lung adenocarcinoma with negative and positive EGFR mutation status of exon 19 and 21, with evaluation parameters are location, numbers, presence of miliary lesion, largest size, component, contrast enhancement, and adjacent edema. A descriptive, retrospective study was performed on 119 lung adenocarcinoma patient with EGFR mutation status who underwent head CT or MRI during January 2018 until December 2019. We found 19 (55.9 %) patients with positive EGFR mutation status of exon 19; 13 (48.1 %) patients with positive EGFR mutation status of exon 21; and 20 (37.0 %) patients with negative EGFR mutation status. The CT and MRI of patients with negative and positive EGFR mutation status of exon 19 and 21 have similar appearance, with most common location at corticomedullary, parietal lobe, multiple, with largest size 1.1-2.5 cm and 2.6 cm, solid-necrotic/cystic component, heterogenous ring contrast enhancement, and perifocal edema

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Keywords: lung adenocarcinoma, EGFR mutation, brain metastasis.

1. Background

Lung cancer is the leading cause of death in the world with mortality rate around 50 % (Yousefi *et al.*, 2017). Adenocarcinoma is the most common type of lung cancer, accounts of more than 40 % of all lung cancer, 60 % of NSCLC and more than 70 % of surgically resected lung cancer (Zeng, 2016). Lung cancer has the potential metastasis to brain even after surgery, radiation, and systemic treatment. The highest incident occurred on the 3rd and 5th year (Mitra *et al.*, 2019). Previous studies stated that most lung adenocarcinoma patients with brain metastasis have positive EGFR mutation status. Lung adenocarcinoma with positive EGFR mutation status of exon 19 showed appearance of brain metastasis lesion with characteristic of small size, large numbers, with minimal adjacent edema. These characteristics are rarely found in brain metastasis of other primary tumors. (Sekine *et al.*, 2012).

2. Method

2.1. Study design

This study is a descriptive, retrospective study which performed at Radiology Diagnostic Department in Diagnostic Center Building of Soetomo General Hospital, Surabaya, collecting data of lung adenocarcinoma patient during Januari 2018 – Oktober 2019.

2.2 Study Population

All patients with pathology result of adenocarcinoma, with examination result of EGFR mutation status, who underwent brain CT Scan and/or MRI.

2.3. Data Collecting Procedure

Data obtained from patients' medical record of Soetomo General Hospital from January 1st, 2018 until December 31st, 2019 which met the inclusion criterias. The data was brain CT and MRI.

2.4. Study Protocol

The researchers identified the medical record data of lung cancer patients, obtain data of lung cancer patients with pathology result of adenocarcinoma and EGFR mutation status examination results, then the raw data of brain CTs and MRIs were evaluated by a neuro-radiologist consultant of Soetomo General Hospital.

2.5. Study Ethics

This study was granted an ethical clearance by the Ethical Committee of Universitas Airlangga / RSUD Dr. Soetomo Surabaya.

3. Result

We found 119 patients consist of 54 (45.4 %) negative EGFR mutation status (wild type), 34 (28.6 %) with positive EGFR mutation status of exon 19, 27 (22.7 %) positive EGFR mutation status of exon 21, 2 (1.7 %) positive EGFR mutation status of exon 20, and 1 (0.8 %) positive EGFR mutation status of exon 19,20. Lung adenocarcinoma patients with positive EGFR mutation status of exon 19 are most common found in female 21 patients (61.8 %), while positive EGFR mutation status of exon 21 and negative mutation status most common in male, found in 15 (55.6 %) and 40 (74.1 %), respectively.

Table 1 : Sample distribution based on EGFR mutation status and gender

EGFR Mutation Status	Frequency	Gender	
		Male	Female
Positive of exon 18	1 (0.8%)	1 (100%)	0 (0.0%)
Positive of exon 19	34 (28.6%)	13 (38.2%)	21 (61.8%)
Positive of exon 20	2 (1.7%)	0 (0.0%)	2 (100%)
Positive of exon 21	27 (22.7%)	15 (55.6%)	12 (44.4%)
Positive of exon 19,20	1 (0.8%)	1 (100%)	0 (0.0%)
Negative (wild type)	54 (45.4%)	40 (74.1%)	14 (25.9%)
Total	119 (100%)	70 (58.8%)	49 (41.2%)

Lung adenocarcinoma patients with positive EGFR mutation status of exon 19 and 21 most common in age group 61 years, found in 52.9% (18 patients) dan 51.9% (14 patients), respectively, while lung adenocarcinoma patients with negative EGFR mutation status most common in age group 51-60 years, 44.4% (24 patients).

Table 2 : Sample distribution based on EGFR mutation status and age group

EGFR Mutation Status	Frequency	Age group				
		30 years	31-40 years	41-50 years	51-60 years	61 years
Positive of exon 18	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Positive of exon 19	34 (28.6%)	1 (2.9%)	4 (11.8%)	5 (14.7%)	6 (17.6%)	18 (52.9%)
Positive of exon 20	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100%)
Positive of exon 21	27 (22.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (48.1%)	14 (51.9%)
Positive of exon 19,20	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	0 (0.0%)
Negative (wild type)	54 (45.4%)	3 (5.6%)	2 (3.7%)	11 (20.4%)	24 (44.4%)	14 (25.9%)
Total	119 (100%)	4 (3.4%)	6 (5.0%)	16 (13.4%)	44 (37.0%)	49 (41.2%)

Lung adenocarcinoma patient with positive EGFR mutation status of exon 19 are the most with brain metastasis found in 19 patients (55.9 %). Lung adenocarcinoma patients with positive EGFR mutation status on exon 21 with brain metastasis are 13 patients (48.1 %). Patients with negative EGFR mutation status are 20 patients (37.0 %).

Table 3 : Sample distribution based on presence of brain metastasis

EGFR Mutation Status	Brain metastasis	
	Positive	Negative
Positif pada exon 18	0 (0.0%)	1 (100%)
Positive of exon 18	19 (55.9%)	15 (44.1%)
Positive of exon 19	0 (0.0%)	2 (100%)
Positive of exon 20	13 (48.1%)	14 (51.9%)
Positive of exon 21	1 (100%)	0 (0.0)
Positive of exon 19,20	20 (37.0%)	34 (63%)

Lung adeocarcinoma patients who received chemotherapy but have brain metastasis are 62.9 % (9 patients) with positive EGFR mutation status of exon 21, 62.2 % (12 patients) with positive EGFR mutation status of exon 19, and 30.0 % (6 patients) with negative EGFR mutation status. There is also 1 patient with positive EGFR mutation status of exon 19,20 with brain metastasis afeter chemotherapy.

Table 4. Sample distribution of brain metastasis based on EGFR mutation status and history of chemotherapy

EGFR Mutation Status	Frequency	History of Chemotherapy	
		Positive	Negative
Positive of exon 19	19 (35.9%)	12 (63.2%)	7 (36.8%)
Positive of exon 21	13 (24.5%)	9 (69.2%)	4 (30.8%)
Negative (wild type)	20 (37.7%)	6 (30.0%)	14 (70.0%)
Positive of exon 19,20	1 (1.9%)	1 (100%)	0 (0.0%)
Total	53 (100%)	28 (52.8%)	25 (47.2%)

In this study, 100 % (6 patients) from CT scan and 92.3 % (12 patients) from MRI of lung adenocarcinoma patients with positive EGFR mutation status of exon 19, the lesion located at the corticomedullary layer. Patients with positive EGFR mutation status of exon 21, 100 % (6 patients) from CT scan and 71.4 % (5 patients) from MRI located at corticomedullary layer. Patients with negative EGFR mutation status, 90 % (6 patients) from CT scan and 70.0 % (7 patients) from MRI located at corticomedullary layer, and 10 % (patients) both from CT and MRI located at leptomeningeal layer.

Table 5. Sample distribution of brain metastasis based on EGFR mutation status and location (brain layer)

Location	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
Corticomedullary	6 (100%)	12 (92.3%)	6 (100%)	5 (71.4%)	9 (90.0%)	7 (70.0%)
White matter	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
Corticomedullary & white matter	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	2 (20.0%)
Leptomeningeal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)

Metastatic lesion location based on brain segment on CT scan, 83.3 % (5 patients) positive EGFR mutation status of exon 19, 66.7 % (4 patients) positive EGFR mutation status of exon 21, and 40.0% (4 patients) negative EGFR mutation status, located at parietal lobe. From MRI we found 86.4 % (11 patients) positive EGFR mutation status of exon 19, 85.7 % (6 patients) positive EGFR mutation status of exon 21, and 40.0 % (4 patients) negative EGFR mutation status, located at parietal lobe.

Table 6. Sample distribution of brain metastasis based on EGFR mutation status and location (brain segment)

Location	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
Frontal	2 (33.3%)	8 (61.5%)	2 (33.3%)	1 (14.3%)	1 (10.0%)	7 (70.0%)
Parietal	5 (83.3%)	11 (84.6%)	4 (66.7%)	6 (85.7%)	4 (40.0%)	9 (90.0%)
Temporal	3 (50.0%)	6 (46.2%)	1 (16.7%)	1 (14.3%)	2 (20.0%)	5 (50.0%)
Occipital	2 (33.3%)	8 (61.5%)	3 (50.0%)	2 (28.6%)	3 (30.0%)	7 (70.0%)
Basal ganglia	1 (16.7%)	2 (15.4%)	1 (16.7%)	0 (0.0%)	1 (10.0%)	0 (0.0%)

Thalamus	1 (16.7%)	1 (7.7%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
Midbrain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
Pons	0 (0.0%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebellum	2 (33.3%)	5 (38.5%)	1 (16.7%)	1 (14.3%)	3 (30.0%)	5 (50.0%)

Numbers of metastatic lesion in this study are differentiate between single or 1 lesion and multiple or more than 1 lesions. From CT scan, we found 83.3 % (5 patients) positive EGFR mutation status of exon 19, 83.3 % (5 patients) positive EGFR mutation status of exon 21, and 50.0 % (5 patients) negative EGFR mutation, have multiple lesions. From MRI we found, 76.9 % (10 patients) positive EGFR mutation status of exon 19 and 90.0 % (9 patients) negative EGFR mutation status, have multiple lesions, while positive EGFR mutation status of exon 21 57.1 % (4 patients) have a single lesion.

Table 7. Sample distribution of brain metastasis based on EGFR mutation status and number(s) of lesion

Number(s) of lesion	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
Single	1 (16.7%)	3 (23.1%)	1 (16.7%)	4 (57.1%)	5 (50.0%)	1 (10.0%)
Multiple	5 (83.3%)	10 (76.9%)	5 (83.3%)	3 (42.9%)	5 (50.0%)	9 (90.0%)

Brain metastatic lesion from CT scan of patients with positive EGFR mutation status of exon 19 size 1.1-2.5 cm found in 66.7 % (4 patients), patients with positive EGFR mutation status of exon 21 size 2.6 cm found in 50.0 % (3 patients), and in patients with negative mutation status we found largest size 2.6 cm found in 50.0 % (5 patients). From MRI of patients with positive EGFR mutation status of exon 19 size 2.6 cm found in 61.5 % (8 patients), patients with positive EGFR mutation status of exon 21 size 2.6 cm and 1.1-2.5 cm found in 42.9 % (8 patients) each, and in patients with negative mutation status we found largest size 2.6 cm found in 70.0 % (7 patients).

Table 8. Sample distribution of brain metastasis based on EGFR mutation status and largest size

Largest size	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
1 cm	0 (0.0%)	2 (15.4%)	1 (16.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
1.1-2.5 cm	4 (66.7%)	3 (23.1%)	2 (33.3%)	3 (42.9%)	4 (40.0%)	2 (20.0%)
2.6 cm	2 (33.3%)	8 (61.5%)	3 (50.0%)	3 (42.9%)	5 (50.0%)	7 (70.0%)
Immeasurable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)

Metastatic lesion component found on CT scan of lung adenocarcinoma patients with positive EGFR mutation status of exon 19 and positive EGFR mutation status of exon 21, all have solid component, while 90.0 % (9 patients) with negative EGFR mutation status have solid component. Cystic component often found from MRI examination, which are 38.5 % (5 patients) positive EGFR mutation status of exon 19, 42.9 % (3 patients) positive EGFR mutation status of exon 21, and 60.0 % (6 patients) negative EGFR mutation status. Necrotic component often found from CT scan, 50.0 % (3 patients) positive EGFR mutation status of exon 1, 66.7 % (4 patients) positive EGFR mutation status of exon 21, and 70.0 % (7 patients) negative EGFR

mutation status. Calcification found on CT scan of 16.7 % (1 patient) with positive EGFR mutation status of exon 21.

Table 9. Sample distribution of brain metastasis based on EGFR mutation status and lesion component

Lesion component	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
Solid	6 (100%)	13 (100%)	6 (100%)	7 (100%)	9 (90.0%)	9 (90.0%)
Necrotic	3 (50.0%)	2 (15.4%)	4 (66.7%)	1 (14.3%)	7 (70.0%)	0 (0.0%)
Cystic	1 (16.7%)	5 (38.5%)	0 (0.0%)	3 (42.9%)	2 (20.0%)	6 (60.0%)
Blood	2 (33.3%)	3 (23.1%)	2 (33.3%)	0 (0.0%)	2 (20.0%)	1 (10.0%)
Calcification	0 (0.0%)	1 (7.7%)	1 (16.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)

Most of contrast enhancement of lung adenocarcinoma with positive EGFR mutation status of exon 19 from CT scan is ring enhancement in 50.0 % (3 patients) and from MRI is heterogenous in 53.8 % (7 patients). In patients with positive EGFR mutation status of exon 21, both CT and MRI the most common enhancement pattern is heterogenous contrast enhancement, 50.0 % (3 patients) and 71.4% (5 patients), respectively. In patients with negative EGFR mutation status from CT scan we found 40.0 % (4 patients) with heterogenous contrast enhancement and 40.0 % (4 patients) with ring contrast enhancement, while MRI examination showed the most common enhancement pattern is ring enhancement found in 40.0 % (4 patients).

Tabel 10. Sample distribution of brain metastasis based on EGFR mutation status and contrast enhancement

Contrast enhancement	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
Heterogenous	2 (33.3%)	7 (53.8%)	3 (50.0%)	5 (71.4%)	4 (40.0%)	3 (30.0%)
Homogenous	1 (16.7%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)
Ring	3 (50.0%)	3 (23.1%)	2 (33.3%)	2 (28.6%)	4 (40.0%)	4 (40.0%)
Ring + heterogenous	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	2 (20.0%)
Ring + homogenous	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Leptomeningeal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)

Patients with positive EGFR mutation status of exon 19 have the most metastatic lesion with perifocal edema, found in 66.7 % (4 patients) from CT and 38.5 % (5 patients) from MRI. Patients with positive EGFR mutation status of exon 21, we found 50.0 % (3 patients) with perifocal edema of metastatic lesion from CT scan while 42.9 % (3 patients) with adjacent tentacle edema. In negative EGFR mutation status, from CT we found 60.0 % (6 patients) and from MRI 50.0 % (5 patients) with metastatic lesion and perifocal edema.

Tabel 11. Sample distribution of brain metastasis based on EGFR mutation status and adjacent edema

Adjacent edema	EGFR Mutation Status					
	Positive of exon 19		Positive of exon 21		Negative (wild type)	
	CT scan	MRI	CT scan	MRI	CT scan	MRI
Perifocal	4 (66.7%)	5 (38.5%)	3 (50.0%)	2(28.6%)	6 (60.0%)	5 (50.0%)
Tentacle	1 (16.7%)	3 (23.1%)	0 (0.0%)	3 (42.9%)	1 (10.0%)	1 (10.0%)
Negative	1 (16.7%)	4 (30.8%)	2 (33.3%)	2(28.6%)	3 (30.0%)	3 (30.0%)
Perifocal + negative	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
Tentacle + negative	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

4. Discussion

Patients distribution in these study is almost similar to the study by Cruz *et al.* in 2011 where male distribution of lung cancer is higher than female and the age group is 65-74 years. Study by Sekine *et al* in 2012 also found that female is significantly higher numbers of lung adenocarcinoma with positive EGFR mutation status of exon 19.

Lung adenocarcinoma patients with brain metastasis, we found 55.9 % (19 patients) with positive EGFR mutation status of exon 19, 48.1 % (13 patients) with positive EGFR mutation status of exon 21, and 37.0 % (20 patients) with negative EGFR mutation status. There is 1 patient with positive EGFR mutation status of exon19,20 also has brain metastasis. Study conducted by Lin *et al* in 2017 also found that lung adenocarcinoma with EGFR mutation tends to metastasis in brain compared to lung adenocarcinoma with negative EGFR mutation or wild type.

Study by Mitra *et al* in 2019 found that lung adenocarcinoma with EGFR mutation significantly caused brain metastasis after multimodality therapy with incidence approximately 33% after 3 years therapy and 43.8 % after 5 years therapy. Thhis study also found that more than half patients with positive mutation status on exon 19 and 21 have brain metastasis even after received chemotherapy but we did not analyze the chemotherapy history further.

Location of brain metastasis lesion, according to literature (Takamori *et al*, 2018) often found in cortico-medullary area due to constricted and acute angles of vessels. Central location of brain metastasis more likely due to significant damage of BBB. According to literature (Takei *et al.*, 2016), leptomeningeal metastasis is a complication of tumor spread damaging the arachnoid sapce, found in 4-7 % patients with solid tumor.

Based on brain segment, metastatic lesion from CT and MRI of patients with negative and positive EGFR mutation status of exon 19 and 21, most found in parietal lobe. Study by Pope in 2018 conducted on NSCLC patients also found the most common location of brain metastasis is parietal and occipital lobe.

Numbers of brain metastasis lesion in this study is differentiate between single or one lesion and multiple or more than one lesion, found in patients with negative and positive EGFR mutation status of exon 19 mostly multiple, while in patients with positive EGFR mutation status of exon 21 mostly single. This result is different from the study by Sekine *et.al* in 2012 which stated that brain metastatis lesion of lung adenocarcinoma in patients with positive EGFR mutation status of exon 19 have a characteristic of multiple lesion compared with patients with negative and positive mutation status of exon 21. The discrepancy may be due to some patients in this study already received chemotherapy.

Study by Sekine *et al* in 2012 found that metastasis lesion of patients with positive EGFR mutation status of exon 19 is smaller compared to patients with negative EGFR mutation status. But from this study

and a study by Takano *et al.* in 2016 found that size of brain metastasis lesion showed no significant difference between EGFR mutation status of lung adenocarcinoma. The study by Shin *et al* in also found no association between lesion size and subtype of EGFR mutation status

According to literature (Oshiro *et al*, 2008) stated that various signal intensity of brain lesion showed variations of components. This is due to the histological component of the tumor. According to Lin *et al* in 2019, necrotic is a result of neovascularisation and rapid growth of tumor followed by lack of blood supply lead to hypoxia of tumor tissue. The hemorrhage in brain metastasis lesion, according to Yoo *et al* in 2010 caused by numbers of factors including endothelial proliferation with vascular obliteration, tumor compression to vessels, vessels necrosis and tumor invasion to vessel wall. Calcified component found mostly from CT of patients with positive EGFR mutation status of 21, 16.7% (1 patient). In the literature (Bahrami *et al.*, 2019) calcification are scarcely found in metastasis lesion, only 1.1 % found during surgery and 6.6 % during autopsy. But some case of brain metastasis with calcified component from lung adenocarcinoma.

Contrast enhancement in patients with negative and positive EGFR mutation status of exon 19 and 21, mostly are ring and heterogenous enhancement. According to literature (Lignelli and Khandji, 2011), contrast enhancement is a result from lack of BBB. The enhancement pattern varied according to the primary tumor. Other literature (Pope, 2018) stated that ring enhancement pattern found in tumor rapidly outgrew the blood supply lead to necrosis of tumor center.

Study by Sekine *et al* in 2012 found that brain metastasis lesion with minimal adjacent edema mostly found in lung adenocarcinoma with positive EGFR mutation status of exon 19. In this study we found adjacent edema in patients with negative and positive EGFR mutation status of exon 19 and 21 mostly are perifocal edema. The discrepancy of this study and previous study maybe due to the population of this study is old cases who already received chemotherapy.

The limitation of this study is the retrospective method, performed in only one hospital, the sample is not divided according to period of brain metastasis lesion, history of therapy, no evaluation of adenocarcinoma histological subtype, no special examination from neurologist so minimal symptoms and slight neurological changes can be detected, and the clinical examination performed by different physician.

5. Conclusion

Prevalence of lung adenocarcinoma with positive EGFR mutation status of exon 19, exon 21, and negative EGFR mutation status, with brain metastasis in Soetomo General Hospital Surabaya from January 1st 2018 until December 31st 2019 are 55.9 %, 48.1 %, and 37.0 %, respectively.

CT scan and MRI appearance of lung adenocarcinoma with positive EGFR mutation status of exon 19, exon 21, and negative EGFR mutation status are similar with most common location in corticomedullary, parietal lobe, multiple, largest size 1.1 – 2.5 cm and 2.6 cm, solid-crotic/cystic component, ring heterogenous contrast enhancement and perifocal edema.

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