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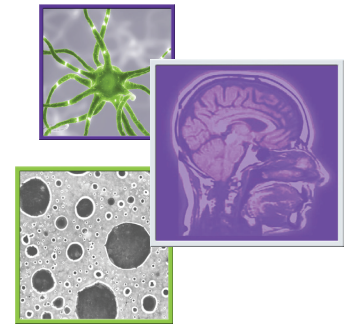

Prognostic factors for patients with newly diagnosed brain metastasis from breast cancer

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Summary points

- Brain metastasis (BM) is associated with a very poor prognosis in breast cancer. Risk factors for developing BM include host factors like race and tumor features of aggressiveness like nonluminal phenotype.
- Prognosis after BM can be predicted by features of tumor at diagnosis and at the BM time. Nonluminal phenotype and high number of brain lesions are associated with poor prognosis after BM.
- Scores combining clinicopathological features like graded prognostic assessment and recursive partitioning analysis can identify those lesions with shortest survival after BM.

SUMMARY **Aim:** This retrospective study determined features associated with brain metastasis (BM) in women with breast cancer. **Patients & methods:** A total of 215 initially early breast cancer cases were included. We reviewed files and CT scan images of BM. **Results:** Median age was 47 years and most of our cases were stage III (58.6%), grade III (62.8%), ER negative (62.3%) and nonluminal (59.1%). Median survival after BM was 4 months. Nonluminal, extracranial disease, time to CNS shorter than 15 months, >three brain lesions and poor breast-graded prognostic assessment and recursive partitioning analysis scores were associated with shorter survival. Adding extracranial disease to breast-graded prognostic assessment score also predicted survival after BM. Radiation response was assessed in 57 patients and response tended to be associated with nonluminal phenotype but not with survival. **Conclusion:** Factors associated with both initial tumor and clinical features at BM time are associated with shorter survival in our Latinas population.

KEYWORDS
• breast cancer • CNS metastases • phenotype • prognostic factor

Brain metastasis (BM) is one of the most serious complications of breast cancer (BC) and produces high morbidity and mortality. Approximately 4–5% of early-stage BC and 8% of locally advanced stage develop BM [1,2]. Several host and tumor risk factors have been associated with a higher risk to develop BM. Host factors could be especially important in predisposition and behavior of BM because malignant cells need to overpass host blood–brain barrier (BBB) and move inside the brain parenchyma [3–10]. Host factors age and race can predict BM development and prognosis [4].

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Table 1. Clinical features of included cases.

Features	Patients (n)	Patients (% of n)
Clinicopathological features at breast cancer diagnosis		
Patients	215	
Median age, years (min–max)	47 (24–80)	
Clinical stage		
I–II	71	33.0
III	126	58.6
Unknown	18	8.4
Histology		
Ductal	209	97.2
Lobular	2	0.9
Medullary	2	0.9
Mixto	2	0.9
Histologic grade		
1–2	75	34.9
3	135	62.8
Unknown	5	2.3
Estrogen receptor		
Negative	134	62.3
Positve	75	34.9
Unknown	6	2.8
HER2 status		
Negative	157	73.0
Positve	55	25.6
Unknown	3	1.4
Phenotype		
Luminal-A	20	9.3
Luminal-B	59	27.4
HER2 enriched	44	20.5
Triple negative	83	38.6
Unknown	9	4.2
Signs and symptoms at brain metastasis		
ECOG at brain metastasis time		
1	121	56.3
2	63	29.3
3–4	15	7.0
Unknown	16	7.4
CT scan image features		
Number of brain lesions		
1–3	118	54.9
>3	77	35.8
Unknown	1	0.5
Carcinomatosis (image or cytology result)	32	14.9
Median diameter of largest lesion, cm (min–max)	2.25 (0.3–9.0)	
Edema	174	80.9
Unknown	20	9.3
Necrosis	32	14.9
Unknown	21	9.8
Hemorrhage	10	4.7
Unknown	20	9.3

ECOG: Eastern Cooperative Oncology Group.

Table 1. Clinical features of included cases (cont.).

Features	Patients (n)	Patients (% of n)
Largest lesion shape		
Nodular	120	55.8
Ringed	34	15.8
Lobulated	11	5.1
Irregular	10	4.7
Cystic	16	7.4
Calcifications	3	1.4
Unknown	21	9.8

ECOG: Eastern Cooperative Oncology Group.

By other side some tumor features can predispose to the development of BM as described by Bos *et al.*, who found a gene expression signature associated with BM [1,4,5].

Aggressive features of tumor as high histologic grade (HG), ER-negative and triple-negative (TN) phenotype have been associated with BM. Most BM appears after 2–3 years of the initial diagnosis of BC and only 20% of patients survive after a year [11]. Treatment with whole brain radiotherapy is the standard of care for most BM and increases median survival in around 5 months [12].

Some prognostic scores combining clinical and pathological features have been developed for predicting survival after BM. Recursive partitioning analysis (RPA) and breast graded prognostic assessment (GPA) score have been tested in series of BC patients with BM. BC in the Latina race has been associated with aggressive features like youth, advanced clinical stage (CS), high HG, ER negative and TN phenotype. Additionally, Latina race also appears to have higher BM rates than Caucasians [13,14]. However, these prognostic indicators have not been validated in Latina race and a comprehensive analysis of variables influencing prognosis after BM development including its response to radiation has not been performed [15–17].

We performed a comprehensive analysis of host and tumor factors affecting prognosis of BC cases with BM in a Peruvian population.

Patients & methods

We retrospectively evaluated every new BC cases attended at the Instituto Nacional de Enfermedades Neoplasicas from 2000 to 2011 and identified those 215 early cases who developed BM. Clinicopathological features were obtained from patient files and brain CT scan image was evaluated by a radiologist of the institute.

Evaluated variables at the time of BC diagnosis included: age, CS, surgery technique, adjuvant treatment, HG, hormone receptor (HR), HER2-status and phenotype [18]. Phenotype was classified into luminal A (ER-positive and progesterone receptor [PgR] >20%, HER2-negative and HG1–2), luminal B (ER-positive and any PgR <20 or HER2+++ or HG3), HER2-enriched (ER and PgR-negative and HER2+++) and TN (ER, PgR and HER2-negative) [19].

Evaluated variables at the time of BM included: ECOG 0–4 (functional status), presence and localization of extracranial disease (ECD) evaluated by image test or clinical evaluation, Time to CNS metastases (TTCNS) and response to radiotherapy according to response evaluation criteria in solid tumors (RECIST) 1.1 criteria [20]. TTCNS was measured from the date of primary diagnosis to the date of BM. Survival time after BM was calculated from the date of BM to the date of death or last follow-up (the last time patient came to the hospital). We also evaluated the prognosis impact of recursive partitioning analysis (RPA; based on status performance, age and presence of ECD) and breast-GPA score (based on status performance, age and phenotype) [21,22].

Association among clinicopathological variables including RECIST response was evaluated through Fisher's exact test and Z-test for two proportions of independent samples.

TTCNS and overall survival (OS) after BM were estimated by using the Kaplan–Meier product-limit method. Association between survival after BM and potential prognostic factors (including GPA and class RPA score) were assessed by using the log-rank or Breslow test in univariate analysis.

Statistical significance was accepted if $p < 0.05$. The data were processed and analyzed using Stata program version 12.0.

Results

We evaluated 215 cases of BM with BC with a median follow-up of 31 months and median survival after CNS metastases of 4 months (0–80 months).

• Features at diagnosis of primary tumor

As Table 1 mentions, we found that median age at BC diagnosis was 47 years. Most cases had ductal histology (97.2%), HG-III (62.8%), ER-negative (62.3%), HER2-negative status (73%), nonluminal (59.1%), TN phenotype (38.6%) and CS-III (58.6%).

Median TTCNS was 22 months (0–86 m) and univariate analysis found that it was shorter in patients with CS III ($p < 0.001$), HG III ($p = 0.0011$), ER-negative ($p < 0.001$), HER2-positive status ($p = 0.0472$), TN ($p = 0.0002$) and nonluminal phenotype ($p < 0.001$) (Table 2).

These features were evaluated in regard to survival after BM, and univariate analysis found that shorter TTCNS ($p = 0.0063$), ER-negative status ($p = 0.0001$), nonluminal ($p < 0.001$) and TN phenotype ($p < 0.001$) predicted shorter survival (Table 3).

Cutoff at 45 years of age was used in Table 2 as we wanted to find out if age could differentiate TTCNs, and a cutoff age to find a significant association was not found. This absence of association is better demonstrated using an age close to the median age of the study series (47.1 years old) – therefore 45 years was decided upon.

Cutoff at 60 years of age was used in Table 3 as we wanted to evaluate those factors that other researchers have found to be associated with BM risk. Breast-GPA score combines the ECOG performance status, tumor phenotype and age with a cutoff of 60 years to give prognosis after BMs.

• Features at the BM event

Performance status ECOG-1 was found in 121 patients (56.3%) and mentally good conscious status at BM event in 164 patients (76.3%). Meningeal symptoms, focalization symptoms and seizures were found in 33.8, 38.6 and 7.1% of the cases, respectively. Most patients had concurrent ECD (68.4%): 50 (23.3%) patients at locoregional area, 41 (19.1%) at bones, 43 (20%) at lungs and 23 (10.7%) at liver. The lungs and the liver are the most frequently compromised places among nonluminal lesions.

Brain image analysis showed one lesion in 41.4% and more than 3 in 35.8%, respectively. Median diameter of largest lesion was 2.25 cm (0.3–9.0) and image of meningeal involvement was found in 14.9%. Important edema, midline shift, necrosis and hemorrhage image

Table 2. Features related to time to CNS metastases.

Features	Patients (n)	Brain metastasis at 2 years (%)	p-value
Age (years):			0.1044
– ≤45	35	40.7	
– >45	55	50.5	
Clinical stage:			<0.001
– I–II	48	72.7	
– III	38	31.4	
Histological grade:			0.0011
– 1–2	41	56.9	
– 3	48	38.1	
Estrogen receptor status:			<0.001
– Positive	51	70.8	
– Negative	41	32.8	
HER2 status:			0.0472
– Positive	19	38.0	
– Negative	74	49.3	
Molecular subtype:			<0.001
– Luminal	52	69.3	
– Nonluminal	38	31.9	
Molecular subtype:			0.0002
– Nontriple negative	67	57.8	
– Triple negative	23	29.5	

Table 3. Features related to survival after brain metastases.

Features	Patients (n)	Survival rate at 1 year (%)	p-value
Age at brain metastases diagnosis (years):			0.1129
– <60	165	20.6	
– >60	27	7.4	
Clinical stage:			0.8690
– I–II	64	21.9	
– III	121	17.4	
Histological grade:			0.2731
– I–II	69	20.3	
– III	126	16.7	
Estrogen receptor status:			0.0001
– Positive	72	31.9	
– Negative	123	12.2	
HER2 status:			0.5627
– Positive	48	18.8	
– Negative	149	19.5	
Phenotype luminal:			<0.001
– Yes	75	33.3	
– No	116	8.6	
Triple-negative phenotype:			<0.001
– No	114	28.1	
– Yes	77	3.9	
ECOG performance status:			0.1376
– 0–1	118	21.2	
– 2	71	15.5	
Time to CNS metastases:			0.0063
– ≤15 months	59	21.4	
– >15 months	140	11.9	
Active extracranial disease:			0.0007
– No	19	47.4	
– Yes	137	11.0	
Number of brain lesions:			0.0275
– 1–3	108	25.0	
– >3	73	11.0	
Edema:			0.2687
– No	18	38.9	
– Yes	163	17.2	
Brain lesion response to radiation following RECIST:			0.8633
– CR	12	41.7	
– PR	16	43.8	
– SD	16	37.5	
– PD	13	46.2	

Time to CNS metastases cut-off of 15 months represents the lower tertile.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; PD: Progressive disease; PR: Partial response; RECIST: Response evaluation criteria in solid tumors; SD: Stable disease.

were found in 80.9, 38, 14.9 and 4.7% of cases, respectively. Most lesions were nodular (55.8%) and circumscribed (91.8%) (Table 1).

These features were evaluated regarding the survival after BM, and univariate analysis found that the presence of ECD (p = 0.0007) and multiple brain lesions (p = 0.0275) predicted shorter survival. Older age than 60 years (p = 0.1129; age cutoff included in breast-GPA score), poor performance status (p = 0.1376), hemorrhage image (p = 0.3159) and brain edema (p = 0.2687) at the BM presentation

Table 4. Comparison of prognostic value of graded prognostic assessment and recursive partitioning analysis scores.

Prognostic score grading	Patients (n)	Survival rate at 1 year (%)	p-value
Breast GPA score:			0.0006
– 0.0–1–0	11	0.0	
– 1.5–2–0	65	4.8	
– 2.5–3.0	36	32.4	
– 3.5–4.0	68	25.8	
Score RPA:			0.0315
– Class 1	15	53.3	
– Class 2	169	16.8	
– Class 3	15	7.7	
Breast GPA score plus ECD:			0.0007
– Non-ECD and score GPA 2.5–4.0	9	55.56	
– Non-ECD and score GPA 0.0–2.0	5	20.0	
– ECD and score GPA 2.5–4.0	72	17.65	
– ECD and score GPA 0.0–2.0	52	2.0	

ECD: Extracranial disease; GPA: Graded prognostic assessment; RPA: Recursive partitioning analysis.

showed a trend to shorter survival after BM (Table 3).

• Evaluation of prognostic scores after BM

Breast-GPA score falls between 0–1, 1.5–2, 2.5–3 and 3.5–4 in 6.1, 36.1, 20 and 37.8%, respectively. RPA score falls in class 1, 2 and 3 in 7.5, 84.9 and 7.5%.

Breast-GPA score ($p = 0.0006$) and RPA score ($p = 0.0315$) predicted a shorter survival after BM. Finally, we evaluated the impact of adding ECD to breast-GPA (divided into two groups for obtaining representative population: 0–2 vs 2.5–4) and found that new groups had also different survival after 1 year of BM: 4.4, 22, 19 and 59.9% ($p = 0.0007$) (Table 4 & Figure 1).

• Features associated with BM response to radiation

Radiation was administered to 197 patients (86.8%) and radiological response according to RECIST 1.1 criteria was evaluated in 57 patients: complete response was observed in 12 patients (21.1%), partial response in 16 (28.1%), stable disease in 16 (28.1%) and Parkinson's disease in 13 (22.8%) (Table 3). No association between RECIST response to radiation and survival was found ($p = 0.8633$). No association between RECIST response to radiation and luminal phenotype was found (0.722). However, luminal phenotype continued to have better prognosis even in this small subset of 57 cases ($p < 0.001$) (Table 5).

When we evaluated factors associated with radiation response, we found that most nonluminal (17/30: 56.7%) and few luminal (12/30: 40.0%) cases obtained BM response ($p = 0.0939$).

Discussion

We initially evaluated the influence of biology from initial breast tumor over BM behavior and similarly to other publications we found that more advanced CS, ER-negative status, nonluminal and TN phenotypes were associated to shorter both TTCNS and survival after BM [1,2,4–10,13]. These factors could predispose cancer cells not only to invade but also to grow inside brain tissue. Remarkably, every mentioned factor has been described as more frequent in Latinas than in Caucasian women as showed in a retrospective analysis we performed in more than 1100 BC Peruvian cases. Higher concentration of these BM-clinical risk factors in Latinas could be responsible for an apparent higher rates of BM we have found in our previous series [13,14].

We also found that HER2-positive status also predisposed to shorter TTCNS but did not predict to shorter survival after BM (despite the fact that patients in our series did not receive anti-HER2 agents at any time), similarly to Anders *et al.* results [4].

The TTCNS under the lower tertile (15 months) was associated with shorter survival in our series. It could represent the fact that tumors with early ability to invade and grow inside CNS had worst prognosis than those lesions that need for further changes in the tumor biology to invade or progress inside brain [4].

The presence of ECD was associated with poor prognosis in our and other series, and indicates that morbidity and mortality caused by systemic disease appear to be relevant even after BM diagnosis [15,21,22].

Tumor features at BM development have been evaluated through features of brain lesion. More than three brain lesions at CT scan were associated (p = 0.04) and brain edema has a trend to shorter survival (p = 0.08). Similarly, Anders *et al.* also found an association between the presence of multiple brain lesions and short survival. This finding correlates with the fact that early detection of occult BM appears to improve survival and decrease mortality [4,17].

Host factors at the time of BM diagnosis like older age (>60 years) tended to have shorter survival, but did not reach significance. This absence of relationship has also been previously reported by Anders *et al.* and Gaspar *et al.* [4,16,21].

Poor performance status at BM, another host factor, tended to have shorter survival but did not reach significance (p = 0.1376), probably because of the small sample size and because most of our patients were at ECOG 1 (60.9%) and alert (76.8%). Sperduto and Gaspar *et al.* have demonstrated that poor performance status are strongly associated to shorter survival after BM in BC as well as in other neoplasms [16,21].

Different groups have developed some prognostic-tools with the combination of clinicopathologic factors [15,22]. Breast-GPA score combines the ECOG status, age and tumor phenotype, and identify a subset with poor survival

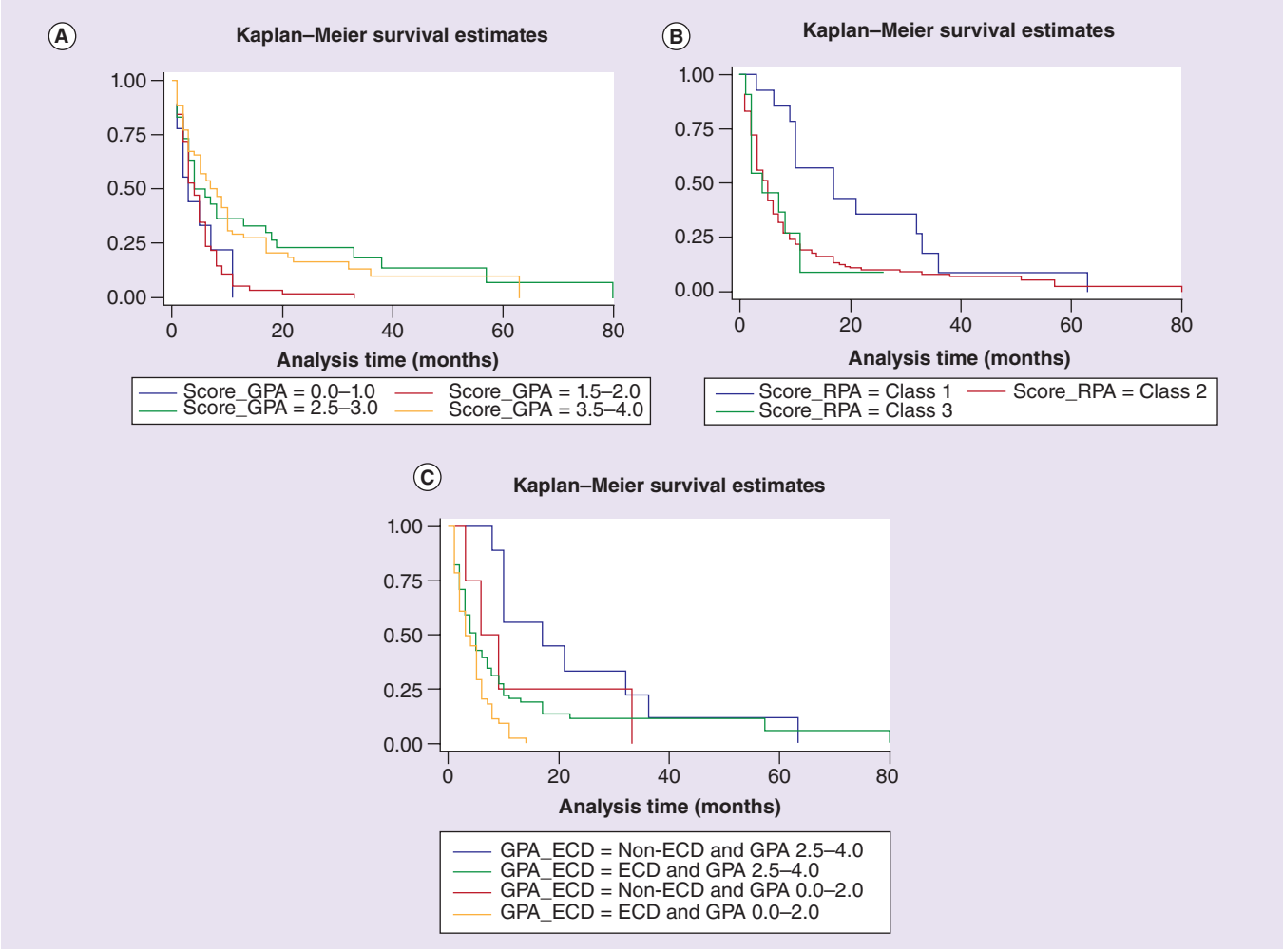

Figure 1. Kaplan–Meier survival curves. Comparison of prognostic value of breast-GPA **(A)**, RPA **(B)** scores and breast-GPA with addition of ECD **(C)** by Kaplan–Meier curves. The y-axes indicate probability from 0 to 1.
ECD: Extracranial disease; GPA: Graded prognostic assessment; RPA: Recursive partitioning analysis.
For color figures, please see online at www.futuremedicine.com/doi/full/10.2217/CNS.15.5

Table 5. RECIST response of brain lesions to radiation.

Response	Luminal A, n (%)	Luminal B, n (%)	HER2, n (%)	TN, n (%)
CR	1 (10.0)	4 (20.0)	2 (15.4)	5 (29.4)
PR	3 (30.0)	4 (20.0)	6 (46.2)	4 (23.5)
SD	2 (20.0)	7 (35.0)	4 (30.8)	5 (29.4)
PD	4 (40.0)	5 (25.0)	1 (7.7)	3 (17.7)
Unknown RECIST	10	39	31	66
Median survival after brain metastasis (months)	7 ± 13.3	6 ± 7.5; $p < 0.001$	4 ± 4	3 ± 2.5

CR: Complete response; PD: Progressive disease; PR: Partial response; RECIST: Response evaluation criteria in solid tumors; SD: Stable disease; TN: Triple negative.

after BM. RPA score combines the first two factors of breast-GPA and adds the ECD factor. We found that both scores achieved significant value in our series. Remarkably, we found also a significant value when we combine breast-GPA score with the presence of ECD.

Our analysis of the subset of patients with postradiotherapy CT scan evaluation found that most nonluminal phenotypes, especially TN BC, achieved BM response and most luminal phenotypes did not; however, it did not achieve significance (we need a larger population to evaluate this trend). However, BM response did not correlate with survival and it appears that even those nonluminal cases with good BM response have short survival. It reminds us the Paradoxical Phenomena previously reported for advanced TN BC that have high response rates to chemotherapy but poor survival [23].

Conclusion & future perspective

In summary, we found that prognosis after BM is affected by features of primary lesion: ER- status, phenotype and TTCNS; as well as features at BM time: the presence of ECD and multiple brain lesions. We found that the addition of the variable ECD to breast-GPA can also identify prognosis after BM. Finally, it appears that BM lesions of most nonluminal BC responded to radiation, but it did not correlate with survival. Further studies are required in the area. I speculate that biological markers in primary lesion that evaluate genes or proteins related to the behavior of brain metastasis as well as functionally image test like PET CT scan with specific markers will be added to these clinico pathological scores in order to improve prognostic value and response prediction accuracy to BM treatment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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