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ORIGINAL RESEARCH

The prognosis and effects of local treatment strategies for orbital embryonal rhabdomyosarcoma: a population-based study

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Introduction: Orbital embryonal rhabdomyosarcoma is a rare childhood malignancy with a good prognosis, but the optimal treatment remains unclear. Using a population-based cancer registry, we assessed the prognoses and survival outcomes of patients with orbital embryonal rhabdomyosarcoma according to the local treatment strategy.

Patients and methods: Patients diagnosed with orbital embryonal rhabdomyosarcoma between 1988 and 2012 as part of the Surveillance Epidemiology and End Results program were included. Univariate and multivariate Cox regression analyses were performed to determine the prognostic factors associated with cause-specific survival (CSS) and overall survival (OS).

Results: In total, 102 patients were included; their median age was 6 years, 78.4% were white, and 56.9% were male. The median tumor size was 30 mm. Of 20 patients with an available histologic grade, the tumors of 90% were poorly differentiated/undifferentiated. Of 92 patients with available surgical and radiotherapy (RT) statuses, 50 (54.3%), 36 (39.1%), and 6 (6.5%) received surgery and RT, primary RT, and primary surgery, respectively. Ninety-five patients (93.1%) received chemotherapy. The 5- and 10-year CSSs of the entire cohort were 94.3% and 92.2%, respectively. The 5- and 10-year OSs were 93.3% and 91.3%, respectively. In 95 patients who were followed up for at least 12 months, there were no significant prognostic factors related to CSS and OS. Furthermore, the local treatment strategy did not significantly affect CSS (P=0.29) or OS (P=0.468).

Conclusion: There is no local treatment of choice for orbital embryonal rhabdomyosarcoma in terms of survival. However, RT is a reasonable alternative treatment to surgery.

Keywords: orbital embryonal rhabdomyosarcoma, survival, radiotherapy, surgery, SEER

Introduction

Orbital embryonal rhabdomyosarcoma is a highly malignant tumor composed of differentiated striated muscle cells.[1] It usually occurs in children aged <10 years.[1] Orbital rhabdomyosarcoma has 3 histologic types: embryonal, alveolar, and pleomorphic. The tumor may appear anywhere in the orbit, but is especially common in the retrobulbar region. Embryonal rhabdomyosarcoma is the most common type of orbital rhabdomyosarcoma in children.[2] In the United States, it is estimated that approximately 350 new cases of rhabdomyosarcoma, including 35 of orbital embryonal rhabdomyosarcoma, are diagnosed each year.[3]

In the 1960s, the overall survival (OS) of orbital rhabdomyosarcoma that received orbital exenteration was 25%–30%. With the development of multidisciplinary treatment involving surgery, radiotherapy (RT), and chemotherapy, the OS has improved to about 90%.[4–10] Reportedly, the 5-year OS of patients with orbital rhabdomyosarcoma

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who receive high-dose chemotherapy is 58.4%.[6] Recently, a therapeutic regimen for orbital embryonal rhabdomyosarcoma was designed using the clinical grouping system of the North American Intergroup Rhabdomyosarcoma Study (IRS) and the tumor-nodes-metastasis (TNM) classification. Its comprehensive, optimal treatment strategies include surgery, RT, systemic chemotherapy, and biotherapy.[3] However, the optimal local treatment for orbital embryonal rhabdomyosarcoma remains unclear. The use of RT in most patients as part of the initial management in the North American approach aims to minimize disease recurrence, whereas the European approach attempts to prevent radiation-induced effects by avoiding the use of upfront RT.[11] In this study, using Surveillance Epidemiology and End Results (SEER) database,[12] we investigated the prognoses and survival outcomes of patients with orbital embryonal rhabdomyosarcoma according to the local treatment strategy.

Patients and methods

We retrospectively collected data from the National Cancer Institute's SEER database,[12] which is a collection of deidentified data from 18 cancer registries in the United States covering approximately 28% of the population. Patients who received a pathologic diagnosis of orbital embryonal rhabdomyosarcoma between 1988 and 2012 were included. The diagnosis was based on the primary tumor site using the third edition of the *International Classification of Diseases for Oncology*. We obtained permission to access the SEER database for research only (reference number: 10269-Nov2015). This study did not require patient consent because the data are deidentified, and this study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University, Xiamen, Fujian, People's Republic of China.

The following demographic and clinicopathologic variables were collected: age; year of diagnosis; race; sex; histologic grade; tumor size; and SEER stage. Local treatment strategies, including primary surgery, primary RT, and surgery plus RT, were also identified.

Univariate and multivariate Cox proportional hazards regression analyses were performed to determine the prognostic factors associated with cause-specific survival (CSS) and OS. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. The statistical data were analyzed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). A P-value of <0.05 was considered statistically significant.

Results

Clinicopathologic characteristics

In total, 102 patients with orbital embryonal rhabdomyosarcoma were included in this study. Their demographic and clinicopathologic factors are shown in Table 1. The median age of the patients was 6 years (range: 1–27 years); 78.4% of them were white, and 56.9% were male. The median tumor size was 30 mm (range: 1–135 mm). Of the 98 patients with an available SEER stage, 68 (66.7%), 23 (22.5%), and 7 (6.9%) were at the localized, regional, and distant stages, respectively. Moreover, of the 20 patients with an available histologic grade, the tumors of 10%, 60%, and 30% were moderately differentiated, poorly differentiated, and undifferentiated, respectively. Tumor stage was available for 45 patients: 77.8% had T2-stage disease. In addition, nodal stage was available for 47 patients, none of whom had nodal metastasis.

Treatment

Of the 100 and 99 patients with an available surgical or RT status, respectively, 56 (56%) and 86 (86.9%) underwent surgical and RT treatment, respectively. Of 92 patients for whom both surgical and RT statuses were available, 50 (54.3%) received surgery and RT, 36 (39.1%) underwent primary RT, and only 6 (6.5%) received primary surgery. There were no significant differences in demographic and clinicopathologic factors between the 3 local treatment groups (Table 2). A total of 95 patients (93.1%) received chemotherapy.

Survival outcomes

The median follow-up period was 99 months (range: 0–311 months). Nine patients died, including 8 patients as a result of malignant tumors and 1 patient as a result of heart disease. In 7 patients at the distant stage of orbital embryonal rhabdomyosarcoma, 1 patient died from heart disease, 1 patient died as a result of malignant tumors, and 5 patients are still alive (range: 52–284 months). The 5- and 10-year CSSs of the entire cohort were 94.3% and 92.2%, respectively. The 5- and 10-year OSs were 93.3% and 91.3%, respectively (Figure 1A and B).

Prognostic factors

We analyzed the prognostic factors of 95 patients who were followed up for at least 12 months. The factors included in our prognostic analysis were age, race, sex, SEER stage, local treatment, and primary tumor size. In the univariate analysis, there were no significant prognostic factors related to CSS

Table 1 Summary of the demographic and clinicopathologic characteristics of 102 patients

Characteristics	n (%)
Age (years)	
≤6	47 (46.1)
>6	55 (53.9)
Years of study	
1988–1992	13 (12.8)
1993–1997	14 (13.7)
1998–2002	21 (20.6)
2003–2007	25 (24.5)
2008–2012	29 (28.4)
Race	
White	80 (78.4)
Black	13 (12.8)
Others	9 (8.8)
Sex	
Male	58 (56.9)
Female	44 (43.1)
Grade (n=20)	
Well-differentiated	0 (0)
Moderately differentiated	2 (10)
Poorly differentiated	12 (60)
Undifferentiated	6 (30)
Tumor size (mm; n=76)	
Median (range)	30 (1–135)
≤5	71 (93.4)
>5	5 (6.6)
SEER stage (n=98)	
Localized	68 (69.4)
Regional	23 (23.5)
Distant	7 (7.1)
Tumor stage (n=45)	
T1	0 (0)
T2	35 (77.8)
T3	7 (15.6)
T4	3 (6.7)
Nodal stage (n=47)	
Negative	47 (100)
Positive	0 (0)
Surgery (n=100)	
No	44 (44)
Yes	56 (56)
Radiotherapy (n=99)	
No	13 (13.1)
Yes	86 (86.9)
Local treatment strategy (n=92)	
Primary surgery	6 (6.5)
Primary RT	36 (39.1)
Surgery + RT	50 (54.3)
Cause of death (n=9)	
Disease of heart	1 (11.1)
Disease of miscellaneous malignant cancer	3 (33.3)
Disease of soft tissue including heart malignant cancer	2 (22.2)
Diseases of kidney and renal pelvis malignant cancer	1 (11.1)
Diseases of brain and other nervous system malignant cancers	1 (11.1)
Diseases of eye and orbit malignant tumor-related diseases	1 (11.1)

Abbreviations: RT, radiotherapy; SEER, Surveillance Epidemiology and End Results.

and OS (Table 3). Furthermore, the local treatment strategy did not significantly affect CSS (log-rank test, P=0.29) or OS (log-rank test, P=0.468; Figure 2A and B).

Discussion

In this study, we used a population-based approach to investigate the clinicopathologic characteristics and prognoses of patients with orbital embryonal rhabdomyosarcoma and assess their survival outcomes according to different local treatment strategies. We observed that the disease occurred much more frequently in younger children and was mostly poorly differentiated/undifferentiated. In addition, we found that the local treatment strategy had no effect on survival outcomes. However, the condition is associated with an excellent prognosis.

The median age of patients diagnosed with orbital rhabdomyosarcoma is reported to range from 4 to 8 years, and its prevalence is higher in boys than in girls.[2,13–15] Van Rijn et al[16] found that the incidence of orbital rhabdomyosarcoma is higher in Caucasians, and that 70% of cases arise in non-Hispanic white individuals. In accordance with this study, our study also confirmed the increased prevalence of the disease in boys and white patients. In addition, most of the patients included in our study exhibited poorly differentiated/undifferentiated malignant tumors, in line with the highly malignant and aggressive characteristics of orbital embryonal rhabdomyosarcoma. However, the patients with orbital embryonal rhabdomyosarcoma included in this study had an excellent prognosis, consistent with previous studies.[2,3,13,17–21] The improved OS of patients with orbital embryonal rhabdomyosarcoma can be attributed to the rapid development of comprehensive, multidisciplinary treatment.

The treatment protocols for orbital rhabdomyosarcoma were designed according to the clinical grouping system of the IRS and TNM classification. In the IRS clinical grouping system, orbital rhabdomyosarcoma is divided into 4 stages, IRS-I, IRS-II, IRS-III, and IRS-IV, and the recommended treatment of orbital rhabdomyosarcoma is based on the results of IRS-V study.[8] Intensive treatment of patients at stages IRS-III and IRS-IV significantly improves their survival outcomes. Currently, the comprehensive treatment strategy for orbital embryonal rhabdomyosarcoma includes local surgery, RT, chemotherapy, and biotherapy. The surgical treatment of orbital rhabdomyosarcoma comprises tumorectomy, biopsy, and needle-aspiration biopsy. Prior to the 1960s, the standard treatment for orbital embryonal rhabdomyosarcoma was whole orbital exenteration, but the survival outcomes were unsatisfactory.[22]

Table 2 Patient characteristics according to local treatment strategies

Characteristics	Surgery (%)	RT (%)	Surgery + RT (%)	*P*-value
Years of study (n=92)				
1988–1992	1 (16.7)	2 (5.6)	7 (14)	0.389
1993–1997	1 (16.7)	4 (11.1)	9 (18)	
1998–2002	2 (33.3)	10 (27.8)	5 (10)	
2003–2007	1 (16.7)	10 (27.8)	13 (26)	
2008–2012	1 (16.7)	10 (27.8)	16 (32)	
Age (years; n=92)				
≤6	2 (33.3)	19 (52.8)	21 (42)	0.536
>6	4 (66.7)	17 (47.2)	29 (58)	
Race (n=92)				
White	4 (66.7)	30 (83.3)	40 (80)	0.343
Black	2 (33.3)	2 (5.6)	6 (12)	
Others	0 (0)	4 (11.1)	4 (8)	
Sex (n=92)				
Male	3 (50)	17 (47.2)	33 (66)	0.198
Female	3 (50)	19 (52.8)	17 (34)	
Grade (n=19)				
Well-differentiated	0 (0)	0 (0)	0 (0)	1.000
Moderately differentiated	0 (0)	1 (16.7)	1 (7.7)	
Poorly differentiated	0 (0)	3 (50)	8 (61.5)	
Undifferentiated	0 (0)	2 (33.3)	4 (30.8)	
Tumor diameter (cm; n=71)				
≤5	5 (100)	23 (88.5)	40 (100)	0.086
>5	0 (0)	3 (11.5)	0 (0)	
SEER stage (n=90)				
Localized	3 (50)	25 (69.4)	35 (72.9)	0.644
Regional	3 (50)	9 (25)	10 (20.8)	
Distant	0 (0)	2 (5.6)	3 (6.3)	
Tumor stage (n=43)				
T1	0 (0)	0 (0)	0 (0)	0.400
T2	1 (50)	13 (86.7)	19 (73.1)	
T3	1 (50)	2 (13.3)	4 (15.4)	
T4	0 (0)	0 (0)	3 (11.5)	
Nodal stage (n=45)				
Negative	2 (100)	17 (100)	26 (100)	–
Positive	0 (0)	0 (0)	0 (0)	

Abbreviations: RT, radiotherapy; SEER, Surveillance Epidemiology and End Results.

In recent studies, approximately 20% of newly diagnosed patients and 50% of patients with recurrence received orbital exenteration.[13,15,23] RT is an important part of multidisciplinary therapy in patients with a poor prognosis after primary surgery.[24–26] Cassady et al[27] reported that high-dose RT decreases disease recurrence after orbital exenteration. In addition, Olivier Pascual et al[7] found that early RT and complete tumorectomy may be important for the treatment of orbital rhabdomyosarcoma. However, patients who undergo primary surgery suffer blindness, disfigurement, and pain, which significantly affects their quality of life. In recent decades, the treatment of orbital embryonal rhabdomyosarcoma has adopted a more conservative approach, combining systemic chemotherapy and RT.[28,29]

In this study, most patients received chemotherapy and 54.3% of patients underwent surgery plus RT; however, the local treatment strategy, including primary surgery, primary RT, and surgery plus RT, had no effect on survival outcomes. Boutroux et al[21] examined 95 patients with orbital rhabdomyosarcoma, including those with embryonal subtype, and found that RT as part of the first-line treatment was a significantly favorable prognostic factor for 5-year event-free survival (EFS), but not for OS. An international collaboration by 4 groups examined 306 patients who received multiagent chemotherapy, 80% of whom also underwent RT: their results showed that local recurrence in the RT group was lower than in the non-RT group (8% vs 44%), whereas the EFSs of RT and non-RT patients were 82% and 53%, respectively

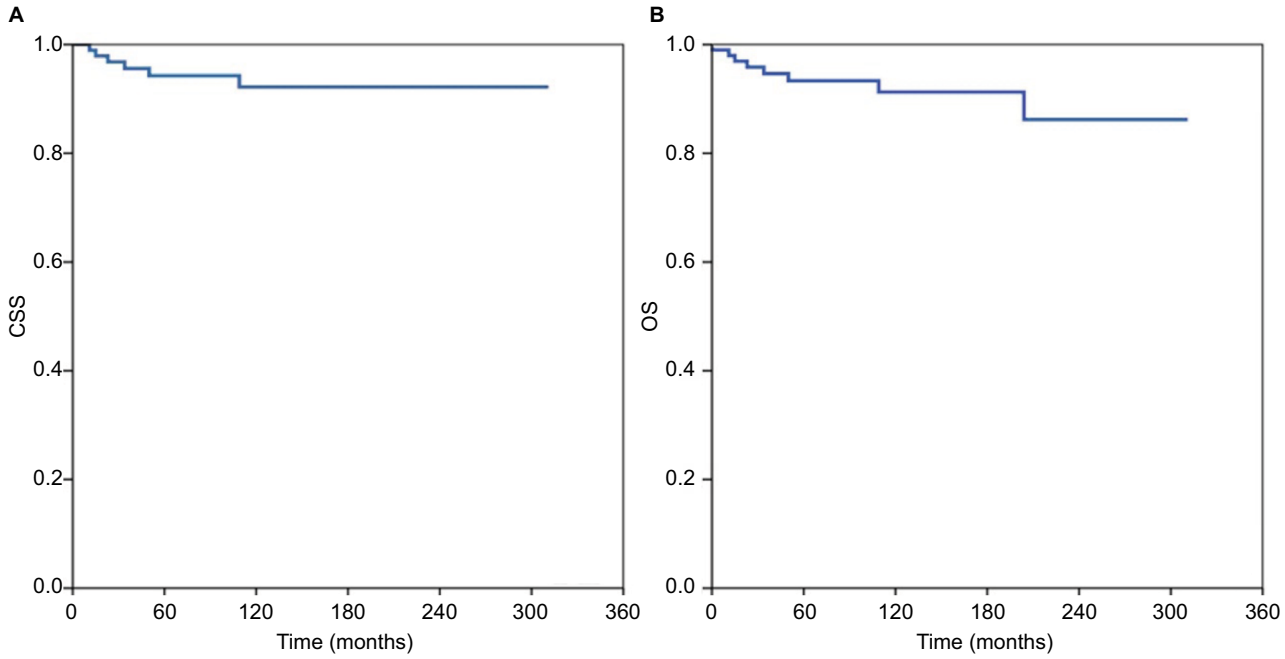

Figure 1 The CSS **(A)** and OS **(B)** of 102 patients with orbital embryonal rhabdomyosarcoma.
Abbreviations: CSS, cause-specific survival; OS, overall survival.

Table 3 Univariate analysis of the CSS and OS of 95 patients who were followed up for at least 12 months

Characteristics	CSS			OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (years)						
≤6	1			1		
>6	0.561	0.094–3.36	0.527	0.417	0.076–2.279	0.313
Race						
White	1			1		
Black	3.543	0.592–21.226	0.166	2.806	0.512–15.373	0.235
Others	–		0.991	–	–	0.990
Sex						
Male	1			1		
Female	0.350	0.039–3.139	0.348	0.285	0.033–2.446	0.252
Tumor diameter (cm)						
≤5	1			1		
>5	0.044	–	0.797	0.044	–	0.797
SEER stage						
Localized	1			1		
Regional	5.370	0.487–59.276	0.170	2.324	0.322–16.761	0.403
Distant	–	–	0.995	–	–	0.992
Local treatment strategy						
Primary surgery	1			1		
Primary RT	0.349	0.032–3.849	0.390	0.385	0.035–4.282	0.438
Surgery + RT	0.135	0.008–2.16	0.157	0.241	0.022–2.675	0.246

Note: "–" indicates no data.
Abbreviations: CI, confidence interval; CSS, cause-specific survival; HR, hazard ratio; OS, overall survival; RT, radiotherapy; SEER, Surveillance Epidemiology and End Results.

(*P*<0.001). However, there was no significant difference in OS between the RT and non-RT patients (87% vs 86%).[30] Therefore, RT has a positive effect on EFS, but not on OS, which may be explained by the different effects of systemic and local treatment after disease recurrence. The choice of optimal local treatment strategies for orbital embryonal rhabdomyosarcoma should consider not only the local control, but also the potential damage to patients. However, the local treatment of orbital embryonal rhabdomyosarcoma remains an issue of controversy between European and North American

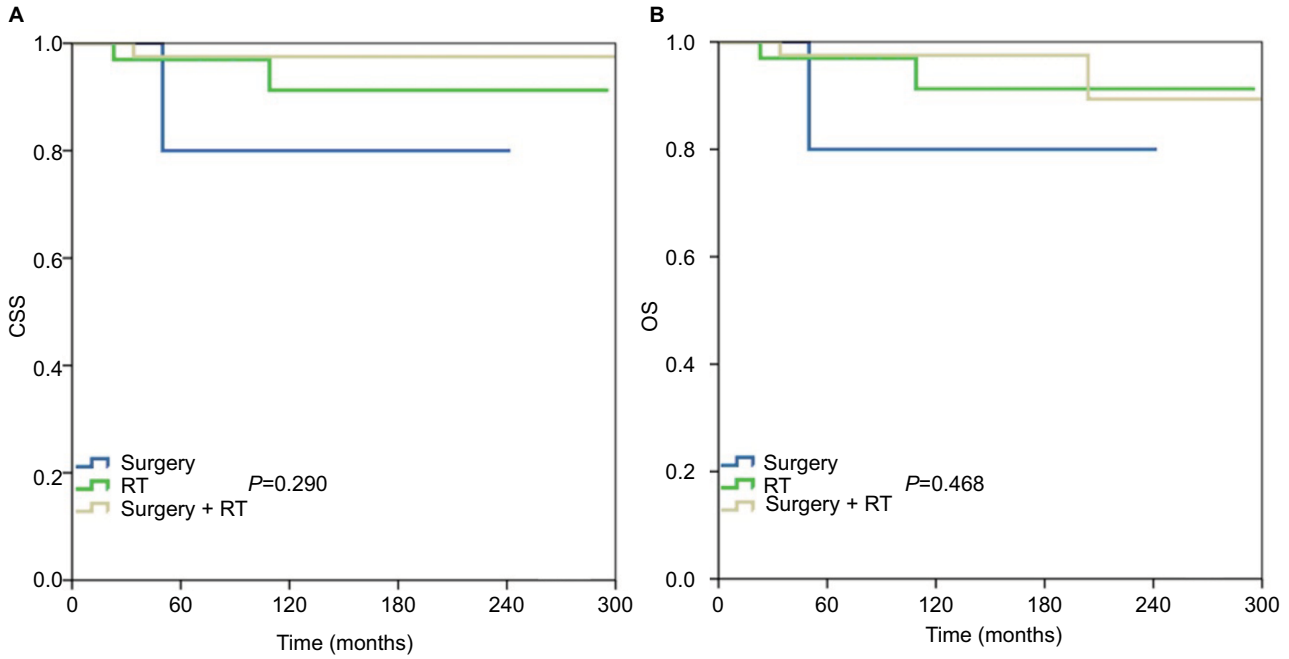

Figure 2 The CSS **(A)** and OS **(B)** of 95 patients with orbital embryonal rhabdomyosarcoma who were treated using different local treatment strategies and followed up for at least 12 months.
Abbreviations: CSS, cause-specific survival; OS, overall survival; RT, radiotherapy.

clinicians: the European approach attempts to avoid radiation-induced sequelae, whereas the North American approach aims to reduce disease recurrence.[12]

Rhabdomyosarcomas are sensitive to RT. Therefore, RT plays an important role in the local treatment of this disease.[31] However, short- and long-term adverse effects commonly occur after RT, such as cataracts, xerophthalmia, chronic keratitis, orbital hypoplasia, corneal ulcers, vitreous hemorrhage, hypopituitarism, retinopathy, and uveitis.[24,27,32] Great progress in RT techniques has been made in recent years. Intensity-modulated RT is superior to conventional RT because of its higher treatment accuracy and better protection of normal organs.[33] In addition, proton therapy may further lower the integral dose and spare normal tissues compared with intensity-modulated RT for orbital embryonal rhabdomyosarcoma.[34] Interstitial brachytherapy is also an effective treatment for children with primary orbital rhabdomyosarcomas.[35,36] Therefore, if treatment-related toxicity can be reduced through improvements in RT techniques, the North American approach may emerge as ethically superior, making RT a reasonable alternative to surgical treatment for orbital embryonal rhabdomyosarcoma.

Limitations

First, the retrospective nature of data from the SEER database and small sample size are major limitations. Second, detailed data related to the IRS clinical grouping system and the chemotherapy and RT regimens used are lacking in the SEER database, and most patients lack data on TNM classification. Therefore, we were unable to include these data and conduct further analyses. In addition, the overall sensitivity of the RT data in the current SEER database is 80%. However, the RT data have a high specificity.[37] Third, we were unable to obtain data on patterns of disease recurrence, complications after RT, and treatment results after recurrence.

Conclusion

Orbital embryonal rhabdomyosarcoma is a rare childhood malignant tumor with an excellent prognosis. There is no local treatment of choice for orbital embryonal rhabdomyosarcoma in terms of survival. However, following rapid progress in RT techniques, RT is a reasonable alternative therapy to surgical treatment. Further studies are needed to confirm our results.

Disclosure

The authors report no conflicts of interest in this work.

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