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ORIGINAL ARTICLE

Treatment results of childhood Ewing's sarcoma of the bone in Serbia

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Summary

Purpose: *The purpose of this study was to present treatment results of childhood Ewing's sarcoma (ES) of the bone in Serbia and to analyze prognostic factors.*

Methods: *We performed a detailed analysis on a series of 107 patients with ES of the bone treated at the Institute for Oncology and Radiology of Serbia between 2000 and 2014, using modern multimodal therapy.*

Results: *Median age at the time of diagnosis was 14 years, with 56.07% of the patients being ≤14 years. There was a male predominance (59.81%). The most common primary sites were pelvis (25.23%), femur (17.76%) and tibia (12.15%). Thirty-four patients (31.78%) had metastatic disease, 17 of which had isolated lung metastases, 9 bone metastases and 8 patients had both. Tumor size ≤ 8 cm had 38.32% and >8 cm had 61.68% patients. Overall, 51.4% patients underwent surgery and radiotherapy as a local treatment modality after neoadjuvant chemotherapy. Radiotherapy alone was performed in 24 patients. The 5-year overall survival (OS) was 43.8%. For patients with localized disease, the 5-year OS was 56.4% and for patients with metastatic disease 17.6%. In patients with initially nonmetastatic disease, age under 14 years, with tumor size <8 cm and a good response to the neoadjuvant chemotherapy, the OS correlated with better outcome.*

Conclusions: *Modern multidisciplinary approach in treatment of childhood ES of the bone in accordance with the recommended pediatric protocols, gives good treatment results. Therapy should be performed in referral centers.*

Key words: *bone, childhood, Ewing's sarcoma, prognostic factor, treatment*

Introduction

Ewing's sarcoma (ES) is the second most common primary bone malignancy in childhood and adolescence [1,2]. The incidence is approximately 3 cases/million/year [3]. Molecular biology studies have shown that this tumor is characterized by a rearrangement of chromosome 22, in the form of an 11;22 translocation in more than 95% of the cases. The gene rearrangement results in the production of an oncogenic transcription factor, e.g. EWS-Fli1 transcription that shows structural variability of potential prognostic relevance depending on chromosomal breakpoint locations [3-6].

ES may involve any bone. About 50% of patients have ES of the extremity, while 20% show

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pelvic tumors. Between 20 and 25% of the patients are diagnosed with metastatic disease [6-9].

Without systemic treatment, more than 90% of patients die of metastases [8,9]. Hence, a ES must be regarded as a systemic disease. Since the 1970s, aggressive cytotoxic treatment regimens have increased survival rates. Multidisciplinary therapy, comprising systemic chemotherapy, local control with surgery, radiotherapy or a combination of them, improved the event-free survival to 69%, with an overall survival (OS) of 72%, for patients with localized disease [8-13]. Unfortunately, the outcome for patients with initially metastatic disease remains poor, with event-free survival of only 28% in recent series. The outlook for patients with recurrent ES is even worse. Thirty to 40% of patients with initially localized ES develop recurrent disease and recurrent patients display a 5-year OS 13% [14-17].

There are numerous factors that might affect the disease outcome. The most important prognostic factor remains the presence of metastasis at diagnosis [7]. Other prognostic factors are age, tumor site, tumor size, and histological response to neoadjuvant chemotherapy. Bone metastases confer a poorer outcome than lung metastases (5-year OS <20% compared with 20-40% respectively) [18-21].

The accepted standard for ES as a rare cancer with complex management is treatment in referral centers [22].

The purpose of this study was to review treatment results of childhood ES of the bone in Serbia, treated in a referral center as well as to analyze prognostic factors.

Methods

Patients and treatment

Between January 2000 and December 2014 107 patients with ES of bone were treated at the Institute for Oncology and Radiology of Serbia (IORS), Department for Pediatric Oncology, using modern multimodal therapy. Inclusion criteria included patients aged ≤19 years with confirmed histopathological diagnosis of ES of bone and patients with no previous malignant disease. All patients were previously diagnosed mostly at the Institute for Orthopedic Surgery "Banjica". Histopathological examination was performed at the Institute for Pathology, Faculty of Medicine, University of Belgrade. Patients underwent neoadjuvant and adjuvant chemotherapy and radiotherapy at the IORS, Belgrade. All these institutions are the national referral centers for the diagnosis and treatment of childhood bone tumors [23,24]. Any pediatric patient suspected of having a bone tumor is admitted to these hospitals to confirm the diagnosis and to plan a treatment strategy. Patients in need for bone marrow transplantation are referred to the Institute for Health Protection for Mother and Child of Serbia "Dr. Vukan Cupic", our referral center for pediatric bone marrow transplantation.

All patients had a biopsy-proven histological confirmation of ES at the time of diagnosis carried out by a pathologist from the referral center. Diagnosis of ES was performed using standard immunohistochemistry methods.

After histological confirmation of the disease, the following clinical and diagnostic procedures were conducted to determine the stage of disease: Physical exam and history, complete blood count, serum chemistry studies, such as lactate dehydrogenase (LDH), magnetic resonance imaging of primary site (MRI), computed tomography (CT) of lung, 99mTc bone scan, bone marrow aspiration, X-ray and PET/CT in selected groups of patients. All medical data were collected from the patients' medical charts. Prior to starting neoadjuvant chemotherapy and every three courses, all patients had standard tumor imaging as indicated. Physical examination and laboratory evaluation were performed prior to each cycle or when indicated.

Treatment was in accordance with EURO E.W.I.N.G 99 and EWING 2008 protocol in 97 patients, and in accordance with protocol EICESS 92 in 10 patients. Neoadjuvant chemotherapy included vincristine, ifosfamide, doxorubicin and etoposide (VIDE) for all patients treated according to EWING protocols [22,25,26].

Outside of specific clinical trials, patients with metastatic disease ought to receive similar therapy to that given for localized disease, with appropriate local treatment of metastases commonly applied as radiotherapy.

Written informed consent for treatment was obtained from all patients or their guardians before starting treatment.

Patients were stratified based on the presence or absence of metastasis at diagnosis, tumor size/volume, and clinical and histological response to neoadjuvant chemotherapy.

Treatment started with neoadjuvant chemotherapy according to the protocol. Local control included surgery, radiation or both. Surgical local and distant control was performed depending on tumor volume, size and site.

Depending on the presence or the type of surgical resection and the histological response to neoadjuvant chemotherapy, radiotherapy (45-54 Gy) was delivered with the option of a boost to 60 Gy depending on the size and site of the primary tumor as well as on the age of patients, according to the protocol (EW 2008). Following local control, patients received vincristine, dactinomycin, and ifosfamide/cyclophosphamide (VAI/VAC), depending on histological response to chemotherapy, according to EWING protocol [15,22,25]. For the patients with metastasis or poor histological response to neoadjuvant chemotherapy, or large tumor volume, the use of consolidation with high-dose chemotherapy (busulfan/treosulfan and melphalan regimens) and autologous stem cell rescue was recommended [14,21,26,27].

Granulocyte colony-stimulating factor (G-CSF) support (5 mcg/kg) was recommended as secondary prophylaxis after an episode of febrile neutropenia in the preceding cycle and in case of profound leukopenia

<1.0x10^9/L. Additionally, patients undergoing consolidation with high-dose therapy and hematopoietic stem cell rescue received G-CSF (10 mcg/kg) for stem cell mobilization [28].

After the completion of treatment, according to the protocol, follow-up examinations were performed every 2-3 months during the first 3 years, every 6 months until the fifth year and yearly thereafter.

Statistics

Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death or to the last follow-up date. Results distributions were estimated using the method of Kaplan/Meier. Factors were compared using Log-Rank test. Descriptive methods (frequencies, percent, mean, median, standard deviation and range) were used to summarize the data. The statistical significance level was set at $p<0.05$. Methods of survival analysis (Kaplan-Meier product-limit method; median with corresponding 95% CI; log-rank test) were used for OS. The statistical analyses were done with the program R version 3.3.2 [29].

Results

Patient characteristics and treatment

Between January 2000 and December 2014, 107 patients with ES of the bone were treated in the Department for Pediatric Oncology of IORS. Follow up data were updated to December 31, 2016.

Median age at the time of diagnosis was 14 years (range 3-19), and 60 patients (56.07%) were ≤14 years. There was a male predominance (64 patients – 59.81%). The mean duration of symptoms was 4.2 months (range 1-36). Overall, 48.6% of ES were localized in an extremity, 25.23% were pelvic and 21.5% had an axial location. The most common primary sites were pelvis (25.23%), femur (17.76%) and tibia (12.15%). Thirty four patients (31.78%) had metastatic disease, 17 of whom had isolated lung metastases, 9 bone metastases and 8 patients had both. Tumor size was ≤ 8 cm in and >8 cm in 66 (61.68%) patients.

The patient clinical and treatment characteristics are shown in Table 1.

The type of local therapy depended on the tumor site, size and age of patient. Overall, 27 (25.23%) patients underwent only biopsy and 80 patients underwent surgery. Six patients (5.61%) had a limb amputation and 58 (54.21%) had wide resection. Fifty-five (51.4%) patients underwent surgery and radiotherapy as a local treatment modality.

Histological response to neoadjuvant chemotherapy was not assessed in 42 (39.25%) patients, mostly in patients who didn't undergo surgery as local treatment and in patients who underwent surgery upfront or at the end of chemotherapy.

Table 1. Patient clinical and treatment characteristics

Characteristics	*n*	%
General	107	100
Gender		
Male	64	59.81
Female	43	40.19
Median age, years,	14	
Range	3-19	
Age, years		
≤ 14	60	56.07
>14	47	43.93
Duration of symptoms, monthly	4.2	
Range	1-36	
Primary tumor location		
Extremities	52	48.6
Pelvic	27	25.23
Axial	23	21.5
Other	5	4.67
LDH at initial diagnosis		
Normal	53	49.53
High	49	45.79
NA	5	4.67
Stage of disease		
Localized	73	68.22
Metastatic	34	31.78
Metastatic location		
Lung	17	15.89
Bone	9	8.41
Lung & Bone	8	7.48
Tumor size, cm		
≤ 8	41	38.32
> 8	66	61.68
Local control modality		
Surgery alone	24	22.43
Radiotherapy alone	24	22.43
Surgery + RT	55	51.40
NA	5	3.74
Histological response		
Good	39	36.45
Poor	26	24.30
NA	42	39.25
Bone marrow transplantation		
Yes	18	16.82
No	89	83.18
Relapse	63	58.88
Local	7	6.54
Distant	32	29.91
Combined	22	20.56
NA	2	1,87

NA: not available

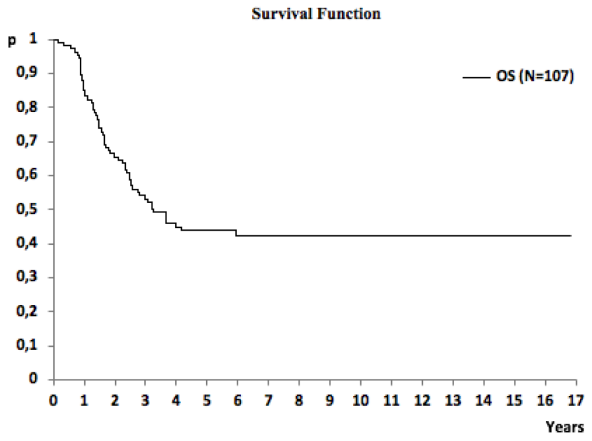

Figure 1. Overall survival in 107 patients with Ewing's sarcoma of the bone.

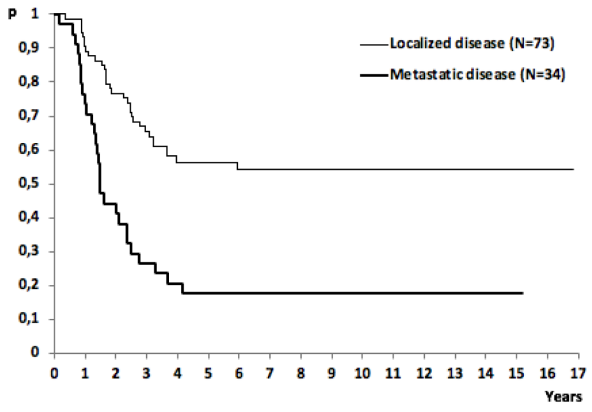

Figure 2. Overall survival in 107 patients according to the stage of disease (p=0.0001).

Table 2. Prognostic factors for 107 patients with Ewing's Sarcoma

Prognostic factors	*n*	*5-year OS, %*	*p value*
Age, years			0.006
≤14	60	53.09	
>14	47	30.07	
Site			
Extremity	52	51.6	0.19
Pelvic	27	17.4	0.0008
Axial	23	51.8	0.30
Tumor size, cm			0.0001
≤ 8	41	67.5	
> 8	66	28.9	
Stage			<0.0001
Nonmetastatic	73	56.4	
Metastatic	34	17.6	
Lung only	17	35.3	
Histological response*			0.02
Good response	39	61.4	
Poor response	26	31.6	

*Available in 65 patients

Radiotherapy alone was performed in 24 (22.43%) patients, in 22 (20.56%) patients as radical treatment and in 8 as preoperative radiotherapy. Eleven out of 25 patients with lung disease at diagnosis, received whole lung radiation therapy.

Eighteen patients (17 with metastases and 1 with large pelvic tumor) received consolidation with high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

There were two toxic deaths during therapy (one during VIDE and one during EVAIA therapy). One patient abandoned therapy after the first cycle of chemotherapy, one after the fourth and one after six cycles and postoperative radiotherapy.

None of the patients were reported to have secondary malignancy.

At cutoff date, December 31, 2016, 47 (43.93%) patients were alive and 60 (56.07%) had died. Sixty-three patients (58.88 %) had a relapse. Relapses were distant in 32 (29.91%) patients, local in 7 (6.54%), combined in 22 (20.56%) and unknown in 2 patients. Fourteen (13.08%) patients developed lung metastases and 20 (18.69%) developed bone metastases.

The 5-year OS for 107 was 43.8% (Figure 1).

For patients with localized disease, the 5-year OS was 56.4% and for patients with metastatic disease it was 17.6%. There were statistically significant differences in OS based on the extent of disease spread (p=0.0001) (Figure 2).

Prognostic factor analysis

The following prognostic factors were evaluated: age, initial tumor size, metastatic disease at diagnosis and histological response to neoadjuvant chemotherapy (Table 2).

OS in patients younger than 14 years, with tumor less than 8 cm, nonmetastatic disease at diagnosis and good histological response to neoadjuvant chemotherapy correlated with better outcome (Figures 2, 3, 4 and 5).

Patients younger than 14 years had 5-year OS 53.09%, which was significantly better than for patients older than 14 years (p=0.006).

Five-year OS in 38.32% of patients with initial tumor size less than 8 cm was significantly better than for 61.68% patients with larger tumor size (67.5% vs 28.9%, p=0.0001).

For patients with localized disease, 5-year OS was 56.4% and for patients with metastatic disease it was 17.6%. There were statistically significant differences in OS based on the extent of the disease spread (p<0.0001).

Patients with isolated lung metastases had better outcome (5-year OS 35.3%) than patients with extrapulmonary metastases (p=0.0014).

Five-year OS in patients with good histological response to neoadjuvant chemotherapy was 61.4%, which was significantly better compared to patients with poor histological response (p=0.02).

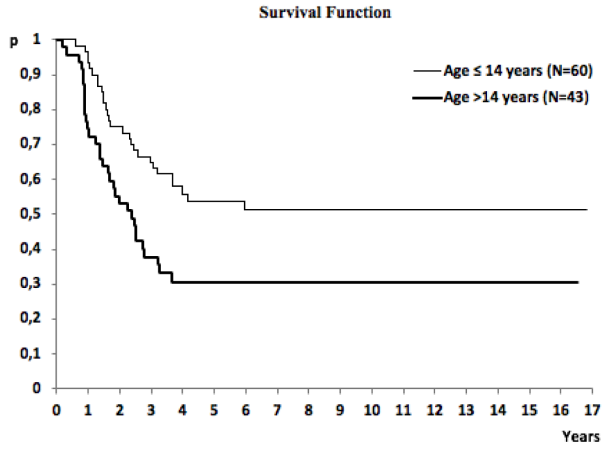

Figure 3. Overall survival in 107 patients according to the age of patients (p=0.006).

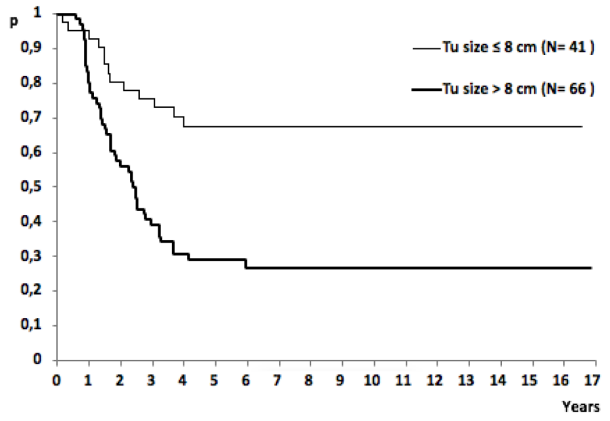

Figure 4. Overall survival in 107 patients according to the initial size of tumor (p=0.0001).

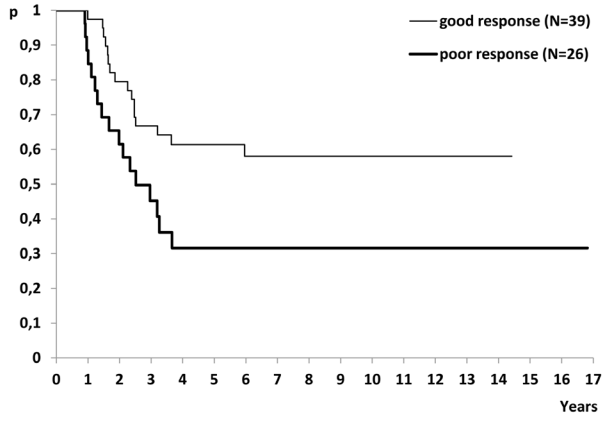

Figure 5. Overall survival in 65 patients according to histological response to neoadjuvant chemotherapy (p=0.02).

Discussion

ES of the bone is a rare cancer that needs complex multimodal approaches in referral centers. Major advances in the treatment of ES have occurred during the last 40 years, however, successful outcomes are dependent on the very careful use of intensive chemotherapy and individualized aggressive local control measures [3,6,12,30].

We have presented an ES study from Serbia, including 107 childhood patients treated at our institute.

Survival rates for ES have increased from 42% in 1975-1979 to 72% in 2003-09. According to literature, 5-year the observed survival rate in 2005-2007 for ES was 71% in Northern Europe, in Central Europe 70%, in Southern Europe 74% and in Eastern Europe 46% [31].

Rodriguez-Galindo et al. in their review of St.Jude Children`s Research Hospital Studies, demonstrated that in a group of 220 patients, the 5-year estimated OS was 63.5% [2].

Five-year OS rate in a study of Sari et al. based on 87 patients was 47% [32].

In our study, including 107 patients, the 5-year estimated OS for patients with ES was 43.8%.

Several limitations must be considered when interpreting our results. These results may be due to the large number of metastatic disease at the time of diagnosis (31.78%). Also, a significant number of patients within the analyzed group had pelvic tumor localization (25.23%) and initial large tumor size (61.68%), which are correlated with poor outcome.

Multiple studies have identified clinical prognostic factors in ES. Some of them have identified distinct risk groups utilizing the following variables: metastatic pattern, age, initial tumor size, tumor site and histological response to neoadjuvant chemotherapy [2,7].

The most important prognostic factor remains the presence of metastasis at diagnosis [2,7,11,16,32].

According to the three major ES trials (EICESS 92, IOR and IESS/SSG), the 5-year OS rate in localized ES ranged from 60 to 70%. Five-year OS was 69% according to the French EW 93 trial. Paulino et al. reported 5-year OS of 57.5% in this group of patients. In a Japanese study, Obata et al. found that the 5-year OS in localized ES was 54.9%. The oncology department from Alexandria reported 5-year OS of 57% for 74 patients with localized disease [33-36].

In our series, the 5-year OS for patients with localized disease at the time of diagnosis was 56.4%. Patients with localized disease did signifi-

cantly better than patients with metastatic disease (56.4 % vs 17.6%, p<0.0001).

The outcome for patients with metastatic disease was very poor. Metastases occurred most commonly in the lungs and bones. For patients with metastatic disease, the only prognostic factor was the pattern of metastasis [14,27,28].

A study by Luksch et al. reported 102 patients with primary metastatic disease and the most common metastatic site were the lungs (86%) and bones (5%) [37]. The Polish Pediatric Oncology group reported that the rate of metastases was 37.87 % at the time of diagnosis [38]. The 5-year OS for this group of patients was 42% and they confirmed that patients with isolated lung metastases have an intermediate outcome (35.3 %). Cotterill et al. demonstrated that for the group with metastases, there was a trend for better survival in those with lung involvement compared with those with bone metastases or a combination of lung and bone metastases [39].

In our group, there were 34 patients (31.78%) with metastatic disease, 17 (50%) of which had isolated lung metastases, 9 had bone metastases and 8 had both.

For our group of 34 patients with metastatic disease, 5-year OS was 17.6%. Our analysis confirmed that patients with isolated lung metastases had a better outcome (5-year OS=35.3%) than patients with extrapulmonary metastases (p=0.0014).

Older age is consistently associated with worse outcome.

The median age of ES in the literature is 15 years [1,2,8,17-21]. In the review of St. Jude Children's Research Hospital, the median age was 13.7 years and the studies by Paulussen et al. reported that the median age was 15 years [2,14].

For ES, the 5-year OS rate has increased from 59% to 78% for children younger than 15 years and from 20% to 60% for adolescents aged 15 to 19 years [1]. The American Cancer Society and the National Cancer Institute reported a 5-year OS rate of 78% for children under the age of 15 and 60% for adolescents aged 15 to 19.

Raciborska et al. in their analysis of prognostic factor in 132 patients didn't confirm that the age at diagnosis was a significant prognostic factor [38].

In our series, the median age of analyzed children was 14 years with male predominance (59.81%) which is in concordance with the majority of other studies.

In our group of 107 analyzed patients, 5-year OS for 56.07% of patients younger than 14 years was 53.09 % and for 43.93% of patients older than 14 years was 30.07%, which is comparable to the majority of data of ES of the bone available in literature.

In most studies, tumor size was found to be significantly associated with improved OS.

The univariate analysis by Rodrigez-Galindo confirmed that in a series of 220 patients, tumor size greater than 8 cm was detected as a significant prognostic factor for poor prognosis. Lee et al. presented results of 725 patients including 51.3% children where large tumor size was also associated with poor prognosis, as they were usually unresectable and associated with metastases. The study of Paulino et al. that included 76 patients, showed significant results. The 5-year OS for patients with tumors ≤ 8 cm was 67.1% and for tumors greater than 8 cm it was 44.5% [2,34,40].

In our study, tumor size ≤ 8 cm was significantly associated with favorable prognosis. Five-year OS in 38.32% of the patients with initial tumor size less than 8 cm was significantly better than for 61.68% patients with larger tumor size (67.5 % vs 28.9%).

Histopathological assessment of tumor necrosis after neoadjuvant chemotherapy had prognostic value. Many studies demonstrated that histological response to chemotherapy of tumors resected after neoadjuvant chemotherapy is one of the most important prognostic outcome factors. The Polish Pediatric Oncology Group reported significantly better 5-year OS in patients with good histological response to neoadjuvant chemotherapy [38].

In our group, out of 65 patients with assessed histological response, 36.45% had a good response and 5-year OS of 61.4%, which was significantly better than for patients with poor response. Our results are comparable to most cooperative trials.

Conclusions

Modern multidisciplinary approach in the treatment of childhood ES of the bone gives good treatment results with long-term survival. Numerous factors affect survival of these patients. According to the results of our study, patients with initially nonmetastatic disease, age under 14 years, with tumor size less than 8 cm, and a good response to the neoadjuvant chemotherapy, belong to the group with good prognosis and they have significantly better chance for survival.

To achieve such high standards of treatment for patients with ES of the bone it is necessary to treat children according to the protocols in referral centers with high level of clinical experience.

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Conflict of interests

The authors declare no conflict of interests.

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