

Prognostic factors affecting survival in metastatic soft tissue sarcoma: an analysis of 110 patients

N. Iqbal¹ · N. K. Shukla² · S. V. S. Deo² · S. Agarwala³ ·
D. N. Sharma⁴ · M. C. Sharma⁵ · S. Bakhshi¹

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Abstract

Background Data on treatment outcome and prognostic factors in patients with metastatic soft tissue sarcoma (STS) are limited in the literature.

Methods A total of 119 patients with metastatic STS treated between June 2003 and December 2012 were analyzed for treatment outcome and prognostic factors.

Results Median age was 37 years (range 2–72 years) with a male to female ratio of 1.5:1. Most common histologic subtypes were synovial sarcoma (36 %) and leiomyosarcoma (16 %). Median tumor size was 12 cm (range 1.6–30 cm). Twenty-four (20 %) patients were treated with multimodality therapy and 80 % patients received systemic chemotherapy alone. At a median follow-up of 10 months (range 1–66 months), the 2-year EFS

and OS were 10 and 19 %, respectively, with a median EFS and OS of 6 and 10 months, respectively. Univariate analysis identified albumin ≤ 4 g/dl ($p = 0.001$), histologic subtypes other than synovial sarcoma ($p = 0.02$), non-extremity tumors ($p = 0.03$) and single modality treatment ($p = 0.03$) as factors predicting poor EFS; however, for OS, hemoglobin ≤ 10 g/dl ($p = 0.02$), tumor size >10 cm ($p = 0.01$) and single modality treatment ($p = 0.04$) were identified as poor prognostic factors. Multivariate analysis identified only serum albumin ≤ 4 g/dl ($p = 0.002$, HR 0.47, 95 % CI 0.29–0.75) associated with poor EFS; however, for OS, hemoglobin ≤ 10 g/dl ($p = 0.009$, HR 0.49, 95 % CI 0.29–0.83), tumor size >10 cm ($p = 0.003$, HR 2.11, 95 % CI 1.28–3.47) and single modality treatment ($p = 0.01$, HR 0.47, 95 % CI 0.25–0.86) emerged as poor prognostic factors.

Conclusions Serum albumin, tumor size, hemoglobin and treatment modality affect survival in metastatic STS.

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✉ S. Bakhshi
sambakh@hotmail.com

¹ Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

² Department of Surgical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

³ Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi 110029, India

⁴ Department of Radiation Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

⁵ Department of Pathology, All India Institute of Medical Sciences, New Delhi 110029, India

Keywords Soft tissue sarcoma · Metastatic disease · Prognostic factors

Introduction

About 10 % patients with soft tissue sarcoma (STS) present with metastatic disease at baseline and 40–60 % patients with high-grade STS develop metastases despite curative local treatment. The median survival after diagnosis of distant metastases is 12 months [1–3]. The development of metastases poses a major clinical problem, as metastatic disease is seldom amenable to a curative treatment. Once metastases are detected, the treatment is based mainly on palliative chemotherapy which produces an overall response rate of about 25 % in the first-line setting [4, 5]. Surgical

resection is well accepted as a standard approach for the treatment of metastases from STS isolated to the lungs, and many studies investigating this technique have reported an overall 5-year survival ranging from 30 to 40 % [6, 7].

Due to paucity of the literature specifically addressing the prognostic factors in metastatic STS, we aimed to study the outcome of patients with metastatic STS treated at our institute and identify prognostic factors affecting survival.

Materials and methods

This was a retrospective analytical study. Medical records of all patients with histologically proven STS treated between June 2003 and December 2012 at our cancer center were reviewed. Those with metastatic disease at presentation to our institute were identified and analyzed. Patients were included whether denovo with metastases or if they had developed metastases after previous treatment for their local site before presenting to our institute. Exclusion criteria were patients who had received chemotherapy before presenting to our institute, those who did not take treatment at our center, those who received ≤ 2 cycles of chemotherapy at our center and were lost to follow-up without progression or event and patients with rhabdomyosarcoma. The histologic diagnosis of all tumors diagnosed outside our centre was confirmed by members of the pathology department of our institute. The tumor characteristics included tumor size, primary tumor site, histology, grade and sites of metastatic disease.

Evaluation of primary lesion was done by magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CECT) depending on the site of lesion. Metastatic workup included CECT scan of thorax, abdomen and pelvis and bone scan wherever required.

Treatment and response evaluation

Treatment consisted of systemic chemotherapy, surgery and radiotherapy. Systemic chemotherapy was the primary therapy given to all patients and different regimens were used depending on the tumor histology. Patients who had complete response (CR) or partial response (PR) at primary site and/or metastatic sites after chemotherapy were taken up for local treatment either in the form of surgery or radiotherapy or both, and surgery of the metastatic sites wherever feasible. The choice of local therapy was made on an individual basis depending on primary tumor site and resectability of tumor after chemotherapy with care to avoid long-term morbidity and disfigurement.

Response to chemotherapy was assessed radiologically after 2 cycles and at completion of therapy. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were defined according to Revised Response Evaluation Criteria in Solid Tumors version 1.1 [8].

Survival analysis and statistics

Patients, tumor and treatment variables were analyzed for their relation to outcome. Any event and death from any cause were used as the end points in this study. Event-free survival (EFS) was calculated from the date of diagnosis to the date of disease progression or death from any cause. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause. All times were calculated from the first registration date to our institute to the last day of follow-up or death from any cause. Data were censored on 31 December 2014. Actuarial survival was determined by Kaplan–Meier analysis. The relations of patient, tumor, and treatment characteristics to outcome were tested by univariate analysis using log-rank. *P* value of ≤ 0.05 was considered statistically significant. Multivariate analysis was performed using Cox proportional hazards model, and only variables that were statistically significant in univariate analysis were included in the final Cox model. Patients who were lost to follow-up (LFU) or had treatment abandonment after 2 cycles of chemotherapy were also included for EFS and OS analysis and outcome in these patients was confirmed by telephonic contact. Treatment abandonment was included for survival analysis in the present study as it has been proposed that patients who were non-compliant and had treatment abandonment should be included in survival analysis for studies from developing nations to provide a true picture of outcome from these countries [9]. STATA/SE 9.0 (Stata-Corp LP, Texas, USA) was used for statistical analysis.

Results

Clinicopathologic profile

Of 950 patients of STS, 215 (23 %) patients presented with metastatic disease. Ninety-six patients were excluded (40 patients who did not take treatment, 45 patients with rhabdomyosarcoma and 11 patients who took ≤ 2 cycles of chemotherapy). So, here we have analyzed 119 patients and their clinicopathologic characteristics are summarized in Table 1. Median age was 37 years (range 2–72 years)

Table 1 Baseline characteristics of 119 patients

Characteristics	Number of patients	Percentage %
Age (years)		
≤35	54	45
>35	65	55
Sex		
Male	71	60
Female	48	40
Time since diagnosis of primary tumor (months)		
<12	92	77
≥12	27	23
Duration of symptoms (months)		
≤6	57	48
>6	62	52
ECOG PS		
0–1	61	51
>1	58	49
Hemoglobin (g/dl)		
≤10	34	28
>10	70	59
Not known	15	13
Median 11 g/dl		
Albumin (g/dl)		
≤4	34	29
>4	54	45
Not known	31	26
Median 4.25 g/dl		
Tumor size (cm)		
≤10	55	46
>10	64	54
Histological subtype		
Synovial sarcoma	43	36
Leiomyosarcoma	19	16
Others	57	48
Tumor site		
Extremity	64	54
Trunk	21	18
Others	34	29
Retroperitoneum	18	15
Visceral	12	10
Head–neck	4	3
Grade		
1	8	7
2	26	22
3	74	62
Not known	11	9
Site of metastases		
Lung alone	76	64
Other than lung alone	13	11
Multiple sites	30	25

Table 1 continued

Characteristics	Number of patients	Percentage %
Number of metastatic sites		
1	89	75
>1	30	25
Type of treatment		
Single modality	95	80
Combined modality	24	20

ECOG Eastern Cooperative Oncology Group, PS performance status

with a male:female ratio of 1.5:1. Median duration of symptoms was 7 months (range 1–120 months). The primary tumor sites were extremity in 54 %, trunk in 18 %, retroperitoneum in 15 %, visceral in 10 % and head–neck in 3 % patients. Most common histologic subtypes were synovial sarcoma in 36 % and leiomyosarcoma in 16 % patients. Other histologic subtypes constituted 48 % of all patients which are shown in Supplementary Table 1. Median tumor size was 12 cm (range 1.6–30 cm) and 109 (92 %) patients had tumor size >5 cm.

Metastatic sites

One hundred and two (86 %) patients had metastases in lungs. Seventy-six (64 %) patients had metastases in lungs alone and 26 (22 %) patients had lung metastases in combination with other sites. Sixteen (13 %) patients had lymph node metastases. Out of 16 (13 %) patients with liver metastases, liver-only metastases were found in 4 patients and combination with other sites was found in 12 patients. Bone metastases were present in 11 (9 %) patients, 2 had bone metastases alone and 9 had in combination with other sites. Other rare sites of metastases were adrenals in 2 patients, brain in 1 patient and skin in 1 patient.

Treatment

Twenty-four (20 %) patients were treated with multimodality therapy and 95 (80 %) patients received single modality, i.e. systemic chemotherapy alone.

Chemotherapy

Systemic chemotherapy was given to all patients with palliative intent and patients having CR/PR at primary or metastatic sites were taken for surgery. The chemotherapeutic regimens used are shown in Supplementary Table 2. Most common regimen consisted of a combination of ifosfamide and doxorubicin in 55 % patients followed by single agent doxorubicin in 31 % patients.

Table 2 Factors affecting EFS and OS in univariate analysis

Characteristics (<i>n</i> = 119)	EFS HR	95 % CI	Median (m)	2-year (%)	<i>p</i> value	OS HR	95 % I	Median (m)	2-year (%)	<i>p</i> value
Age (years)										
≤35 (<i>n</i> = 54)	1	0.76–1.62	6	10	0.56	1	0.82–1.77	12	24	0.32
>35 (<i>n</i> = 65)	1.1		5	10		1.2		9	17	
Sex										
Male (<i>n</i> = 71)	1	0.75–1.61	6	8	0.59	1	0.91–1.96	11	21	0.13
Female (<i>n</i> = 48)	1.1		5	10		1.3		7	19	
Time since diagnosis of primary tumor (months)										
<12 (<i>n</i> = 92)	1.1	0.69–1.72	5	11	0.66	1.2	0.74–1.87	10	20	0.47
≥12 (<i>n</i> = 27)	1		6	10		1		10	16	
Duration of symptoms (months)										
≤6 (<i>n</i> = 57)	1	0.57–1.21	4	10	0.32	1.02	0.68–1.50	8	21	0.92
>6 (<i>n</i> = 62)	0.83		7	11		1		11	20	
ECOG PS										
0–1 (<i>n</i> = 61)	1	0.93–1.97	8	11	0.09	1	0.82–1.80	14	21	0.3
>1 (<i>n</i> = 58)	1.36		4	8		1.22		7	17	
Hemoglobin (g/dl)										
≤10 (<i>n</i> = 34)	1	0.39–1.08	4	10	0.08	1	0.33–0.93	8	11	0.02
>10 (<i>n</i> = 70)	0.66		6	12		0.56		13	25	
Serum albumin (g/dl)										
≤4 (<i>n</i> = 34)	1	0.29–0.75	3	6	0.001	1	0.45–1.14	6	12	0.14
>4 (<i>n</i> = 54)	0.47		8	12		0.72		13	24	
Tumor size (cm)										
≤10 (<i>n</i> = 55)	1	0.93–2.01	5	15	0.09	1	1.12–2.43	14	28	0.01
>10 (<i>n</i> = 64)	1.37		5	5		1.65		7	10	
Histological subtype										
Synovial sarcoma (<i>n</i> = 43)	1	1.06–1.61	10	14	0.02	1	0.89–1.36	14	21	0.62
Others (<i>n</i> = 76)	1.3		5	8		1.1		8	18	
Tumor site										
Extremity (<i>n</i> = 64)	1	0.84–1.27	6	11	0.03	1	0.78–1.21	10	17	0.68
Non-extremity (<i>n</i> = 55)	1.03		4	5		0.97		8	15	
Grade										
1 (<i>n</i> = 8)	1	0.58–1.07	4	12	0.24	1	0.65–1.20	5	25	0.46
2 (<i>n</i> = 26)	1		4	10		1		9	27	
3 (<i>n</i> = 74)	0.79		7	9		0.88		12	20	
Site of metastases										
Lung alone (<i>n</i> = 76)	1	0.79–1.21	5	12	0.29	1	0.71–1.11	11	17	0.52
Other than lung alone (<i>n</i> = 13)	1		4	8		1		7	23	
Multiple sites (<i>n</i> = 30)	0.97		6	9		0.89		12	23	
Number of metastatic sites										
1 (<i>n</i> = 89)	0.87	0.56–1.34	5	10	0.5	0.78	0.49–1.21	10	18	0.26
>1 (<i>n</i> = 30)	1		6	8		1		12	23	
Type of treatment										
Single modality (<i>n</i> = 95)	1	0.32–0.86	4	6	0.006	1	0.37–0.98	8	17	0.04
Combined modality (<i>n</i> = 24)	0.65		9	20		0.61		18	28	

ECOG Eastern Cooperative Oncology Group, PS performance status, EFS event-free survival, OS overall survival, HR hazard ratio, CI confidence interval

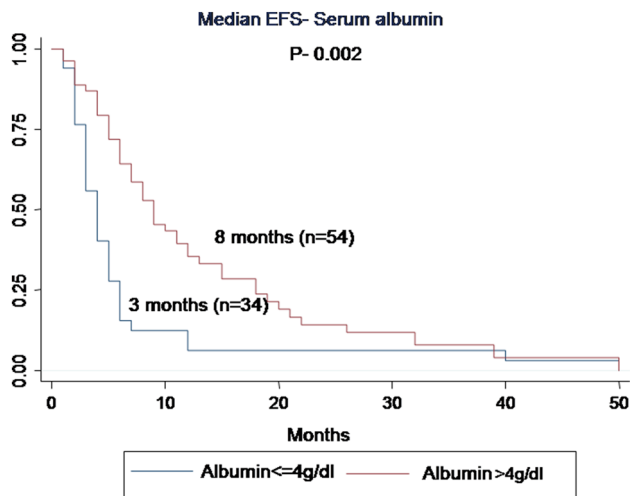


Fig. 1 EFS of whole cohort based on serum albumin

Surgery

Surgery was done in 24 (20 %) patients, out of which 10 patients underwent wide local excisions and amputation was performed on 14 patients. Metastasectomy for lung metastases was performed on 6 patients.

Radiotherapy

Eighteen (15 %) patients received external beam radiotherapy. Definitive radiotherapy in the dose of 45–60 Gy was received by 4 patients and palliative radiotherapy in the dose of 8–36 Gy was received by 14 patients.

Response and toxicity

Overall, 9 (8 %) patients achieved CR, 18 (15 %) patients achieved PR and 38 (32 %) patients had SD. The overall response rate with chemotherapy was 23 % (including CR and PR). Fifty-four (45 %) patients developed progression on treatment. Twenty-one (18 %) patients developed Grade

I and II and 3 (2.5 %) patients developed Grade III and IV toxicities. The most common toxicity was myelosuppression in 18 patients and 1 patient died due to febrile neutropenia.

Survival

At the end of last follow-up, 107 patients were dead (98.5 % deaths due to disease progression), 6 patients were alive (1 in CR and 5 with disease) and follow-up information for 6 patients was not known.

Median follow-up was 10 months (range 1–66 months). The 2-year EFS and OS were 10 and 19 %, respectively, with a median EFS of 6 months and a median OS of 10 months (Supplementary Figs. 1, 2).

Prognostic factors

Univariate analysis

For EFS, albumin ≤ 4 g/dl ($p = 0.001$), histologic subtypes other than synovial sarcoma ($p = 0.02$), non-extremity tumors ($p = 0.03$) and single modality treatment ($p = 0.03$) emerged as poor prognostic factors. However, for OS, univariate analysis identified hemoglobin ≤ 10 g/dl ($p = 0.02$), tumor size >10 cm ($p = 0.01$) and single modality treatment ($p = 0.04$) as poor prognostic factors (Table 2).

Multivariate analysis

Multivariate analysis for EFS identified only serum albumin ≤ 4 g/dl ($p = 0.002$, HR 0.47, 95 % CI 0.29–0.75) associated with poor EFS (Fig. 1), whereas for OS, tumor size >10 cm ($p = 0.003$), hemoglobin ≤ 10 g/dl ($p = 0.009$) and single modality treatment ($p = 0.01$) emerged as poor prognostic factors (Table 3) (Fig. 2a, b, c).

Table 3 Factors affecting EFS and OS in Multivariate analysis

Characteristics	Variables ($n = 119$)	EFS HR	95 % CI	p value	OS HR	95 % CI	p value
Serum albumin (g/dl)	≤ 4 (34)	1					
	>4 (54)	0.47	0.29–0.75	0.002			
Hemoglobin (g/dl)	≤ 10 (24)				1		
	>10 (60)				0.49	0.29–0.83	0.009
Tumor size (cm)	≤ 10 (55)				1		
	>10 (64)				2.11	1.28–3.47	0.003
Treatment modality	Single (95)				1		
	Combined (24)				0.47	0.25–0.86	0.01

EFS event-free survival, OS overall survival, HR hazard ratio, CI confidence interval

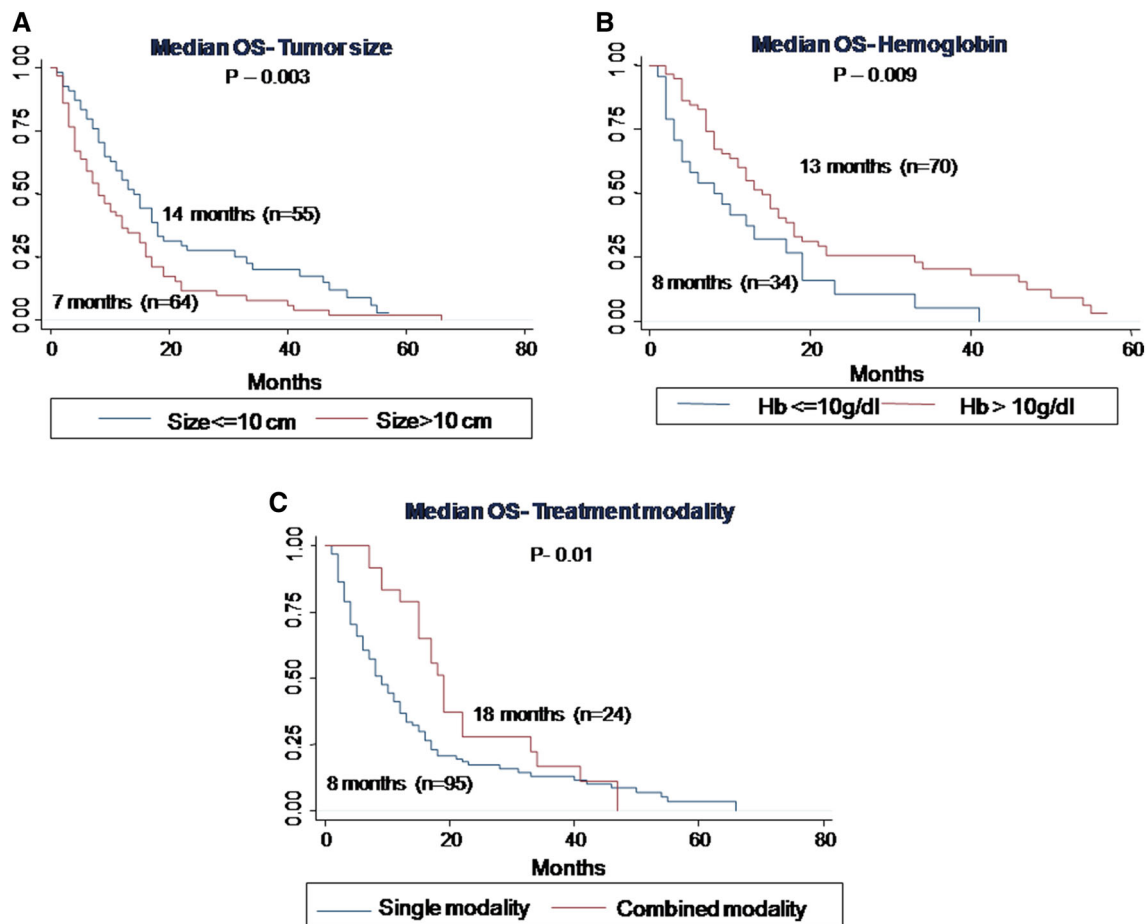


Fig. 2 Overall survival of whole cohort. **a** Based on tumor size, **b** based on hemoglobin and **c** based on treatment modality

Discussion

The median survival of our cohort was 10 months with 2-year OS of 19 % which is comparable to the published literature [1, 10, 11]. Ifosfamide and doxorubicin combination was most commonly used in our study and an overall response rate of 23 % was found which is consistent with the literature [12–17]. Due to varied histologic subtypes in our cohort with small number of patients in each group, it is difficult to make statistical comparisons between different chemotherapeutic regimens. Most studies on STS are severely hampered by the admixture of a variety of histologic subtypes, making it difficult to assess the clinical activity of any given treatment.

Surgical resection for the treatment of pulmonary metastases has shown improvement in 5-year survival ranging from 30 to 40 % [6, 7, 11, 18]. Since the number of patients undergoing pulmonary metastasectomy in our study was very less, it is difficult to draw any conclusion on its benefit.

Little is known about the prognostic factors in metastatic STS. There is only one previous study by Van Glabbeke

et al. [1] specifically addressing this cohort of patients which recognized factors such as extrapulmonary metastases and histologies like leiomyosarcoma and malignant fibrous histiocytoma to be associated with poor prognosis whereas good performance status, absence of liver metastases, low histopathologic grade, long time since diagnosis of the primary tumor, few metastases, and young age had favorable outcome [1]. We found low serum albumin, tumor size > 5 cm, low hemoglobin and single modality treatment as adverse prognostic factors in this group.

Serum albumin has been described as an independent prognosticator of survival in various cancers [19–23]. A study by Barreto-Andrade et al. [24] analyzing a group of 61 patients with STS found serum albumin as independent prognostic factor of survival in these patients. Another study by Biswas et al. [25] done in metastatic Ewing's sarcoma found low serum albumin as a poor prognosticator of disease outcome. Our study confirms the association of low serum albumin level with poor survival in metastatic STS.

Tumor size is well recognized as an independent prognostic indicator in localized STS and is a determinant of

both local recurrence as well as metastatic disease [3, 24, 26, 27]. Bauer et al. [3] found larger primary tumors in patients with metastatic STS than patients with localized disease: median 11 cm versus 7 cm, respectively; however, the prognostic impact of tumor size in metastatic STS was not found. Our study is the first of its kind which establishes tumor size as an independent prognostic factor for metastatic disease. The relatively poorer survival in our cohort might be explained by large tumor size; notably 98 % of this cohort had tumor size >5 cm and the median tumor diameter was 12 cm.

Low hemoglobin level before surgery was found to have negative prognostic impact on clinical outcome in patients with localized STS in a study by Szkandera J et al. [28]. Our study confirms the poor impact of low baseline hemoglobin on survival in metastatic disease as well.

The benefit of surgery for primary site in metastatic STS is not clear. However, clear benefit of treatment for primary tumor site was found in our study as patients who underwent multimodality treatment had better survival rates than patients who received systemic chemotherapy alone (28 vs 17 %, p value = 0.04). This study emphasizes upon addressing the primary tumor site in metastatic disease as well either by surgery or radiotherapy. However, more studies are required to draw any meaningful conclusion.

In conclusion, this is a large single-institutional study on metastatic STS which identifies serum albumin, tumor size, hemoglobin and treatment modality as factors predictive of outcome in metastatic disease.

Conflict of interest None.

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