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# SYNOVIAL SARCOMA AMONG ADULTS: FROM EPIDEMIOLOGY TO CLINICAL PRESENTATION, CURRENT DIAGNOSTIC STANDARDS, TREATMENT METHODS AND PROGNOSIS

***Jakub Bulski[1]*** ✉, ***Filip Maj[1]***, ***Karol Sornat[1]***, ***Agata Estreicher[2]***, ***Anna Klasa[3]***, ***Aleksandra Sobaś[1]***, ***Kamil Biedka[2]***, ***Oliwia Ziobro[2]***, ***Katarzyna Błaszczyk[2]***

[1]*Collegium Medicum, Jan Kochanowski University, Kielce, Poland*
[2]*Wroclaw Medical University, Wroclaw, Poland*
[3]*The University Hospital in Krakow, Krakow, Poland*

✉ ***jakub.bulski@icloud.com***

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## ABSTRACT

**Aim:** This article aims to comprehensively analyse the available literature on synovial sarcoma (SS), focusing on its pathogenesis, epidemiology, clinical presentation, diagnostic strategies, treatment approaches, and emerging therapeutic research.

**Methods:** A systematic literature search was conducted in PubMed, ClinicalKey and Google Scholar using the keywords *synovial sarcoma* and *soft tissue sarcoma*. A total of 104 peer-reviewed articles published within 1914-2025 were selected based on relevance, methodological quality and contribution to the field.

**Results:** SS is a rare soft tissue sarcoma (STS), accounting for 2–4.2% of all STS cases. It predominantly affects adults aged 20–44 years, with 10% of cases occurring among children. The tumor most commonly arises in the extremities, particularly the lower limbs, and typically presents as a painless mass. Diagnosis relies on magnetic resonance imaging (MRI) followed by biopsy, histopathological analysis, and molecular testing for SYT-SSX fusion genes. The mainstay of treatment is en bloc surgical resection, with radiotherapy and chemotherapy (e.g., doxorubicin + ifosfamide) serving as adjunct therapies in select cases.

**Conclusions:** SS presents a significant clinical challenge due to its rarity, nonspecific symptoms, and aggressive nature. Early detection of tumors, particularly those <5 cm, is crucial for improving outcomes. Multidisciplinary management in specialized sarcoma centers is essential for optimizing treatment strategies. Further research is needed to explore targeted therapies, immunotherapy, and molecular-driven treatment approaches to improve long-term prognosis.

**Keywords:** synovial sarcoma, soft tissue sarcoma, diagnosis, treatment, prognostic factors, targeted therapy

## INTRODUCTION

Sarcomas are a rare and heterogeneous group of malignant neoplasms originating from mesenchymal

tissue, accounting for only 1% of all malignancies in the human population [1]. They are traditionally classified into bone sarcomas and soft tissue sarcomas (STS) [2]. Among STS, which have an estimated incidence of 3.6 per 100,000 people, synovial sarcoma (SS) represents a distinct entity with unique molecular and clinical characteristics [3].

The World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone (4th edition) recognizes over 100 histological subtypes of STS, including SS, which is the focus of this article. [4]. The term *synovial sarcoma* was first introduced by Jones and Whitman in 1914 [5]. Initially, SS was believed to arise from the synovial membrane; however, subsequent research has demonstrated that its true origin lies in primitive mesenchymal tissue, with no direct relation to synovial structures [6].

A major breakthrough in understanding SS occurred in the 1990s, with the discovery of its hallmark chromosomal translocation t(X;18) [7]. This translocation leads to the fusion of the SYT gene with either SSX1 or SSX2, forming the SYT-SSX fusion protein, which plays a critical role in tumorigenesis [8,9]. While this fusion protein is known to regulate gene transcription, its exact oncogenic mechanism remains incompletely understood [10].

Histologically, SS is classified into three subtypes:

- Monophasic (61.2%) – composed primarily of spindle cells.
- Biphasic (37.7%) – containing both spindle and epithelial-like cells, associated with a better prognosis.
- Epithelioid (1.1%) – a rare and aggressive variant with the poorest prognosis, more frequently observed among Black patients [11].

Considering SS's complex biology, diagnostic challenges, and aggressive nature, a comprehensive review of its epidemiology, clinical presentation, and current treatment strategies is essential. This article aims to analyse key aspects of SS, with particular focus on diagnostic imaging techniques, histopathological evaluation, and therapeutic approaches. Additionally, prognostic factors influencing treatment outcomes will be discussed based on the latest research and guidelines.

## MATERIALS AND METHODS

To conduct a thorough evaluation of the available data, we performed a literature search in the PubMed, Clinical Key, and Google Scholar databases using the keywords *synovial sarcoma* and *soft tissue sarcoma*. Based on the search results, we selected 104 peer-reviewed articles published within 1914-2025 that, in our opinion, most accurately describe the issue under investigation and provide valuable new insights into the topic.

## RESULTS

### EPIDEMIOLOGY AND LOCALIZATION

Among patients suffered from STS, depending on the sources, SS accounts only for 2% to 4.2% [3,12]. It is significant that the incidence of SS has been steadily increasing, from 0.906 per 1,000,000 people in the population in 1984 to 1.548 in 2012 [13]. Approximately 40% of SS cases involve patients aged 20 to 44, while another high-risk group consists of individuals aged 45 to 64. It is worth noting that among all patients diagnosed with SS, those under the age of 19 account for less than 10% [14]. Although SS is rare, it represents the most common non-rhabdomyosarcoma STS in the pediatric population [15].

In terms of localization, SS most frequently occurs in the limbs, with the primary tumor site commonly found in the distal regions of the lower extremities [16,17]. In rare cases, the primary lesion may be located within the joint cavity [18–20]. Less common than extremities locations include the trunk, head and neck, and chest [21,22]. However, it is important to note that SS can also occur in locations not typically recognized as primary sites for this tumor. Current literature includes approximately 70 documented cases of SS originating within the gastrointestinal tract. Among these, a study by Zhang et al. described a rare case of rectal SS presenting with rectal bleeding [23]. Another case report by Yalcin et al. described a 13-year-old boy with SS localized in the tonsil, further highlighting the diverse and atypical presentation sites of this malignancy [24].

### CLINICAL PRESENTATION

The clinical presentation of SS largely depends on the tumor's location and stage of progression [25]. The most common clinical symptom observed in patients is the appearance of a painless mass at the site of the primary lesion [26]. It is important to consider that a significant proportion of patients do not present with this symptom. In a study of pediatric patients with SS Chotel et al. reported that 30.3% of participants did

not exhibit any kind of visible mass. This study, however, was limited by a small sample size of 35 cases [27]. In a significant number of cases, the appearance of visible changes in the limbs is preceded by pain unrelated to injury at the site of the primary lesion, which should clearly prompt clinicians to consider a diagnosis of SS. De Silva et al. reported that in approximately 30% of SS patients, pain occurs before the appearance of tissue swelling or a palpable mass. In contrast, this symptom was present in only 3,6% of patients with other sarcomas ($p < 0.001$) [28]. In cases of periarticular localization, the tumor may cause a limitation in joint mobility [27]. As previously mentioned, atypical localization of SS can lead to unusual symptoms. Steinstraesser et al. reported the case of a 31-year-old man who presented to the hospital with classic symptoms of carpal tunnel syndrome lasting for three months. During surgery, a 2,5 cm mass was found within the carpal tunnel, which, after removal and pathological examination, was identified as SS [29]. The nonspecific symptoms and diagnostic challenges associated with SS are well illustrated by the case of a 39-year-old woman described by Hatano et al., who, despite clinical symptoms and multiple hospitalizations, remained without a correct diagnosis of SS for approximately 20 years [30].

More than one-third of patients with SS develop distant metastases [31]. The authors of the METASYN study conducted by the French Sarcoma Group demonstrated that among these individuals, the lungs are the most common metastatic site, accounting for 76,1% of cases, followed by lymph nodes (5.9%), pleura (5.1%), bones (4.3%), peritoneum (2.9%), and liver (1.6%) [32]. Krieg et al. report that metastases typically appear 5.7 years after diagnosis, but some cases occur more than 10 years later. The authors recommend that follow-up care for these patients be extended beyond 10 years [33].

## DIAGNOSTTIC METHODS

The initial imaging diagnosis of SS, like other STS, should begin with a conventional X-ray and ultrasound examination of the suspicious area [34].

### X-ray

The radiological features typically associated with SS include a soft tissue mass (67%), soft tissue calcifications (20%), and bony erosion (20%) [35].The main radiographic feature suggesting SS is the presence of a mineralized mass near, but not within, a joint, particularly in a young adult [36].

### Ultrasound

Ultrasound is a valuable imaging modality in the initial diagnostic evaluation of soft tissue masses. It allows for the differentiation between fluid-filled lesions, for which further diagnostic work-up is typically not required, and solid masses. Additionally, ultrasound plays a role in guiding biopsy procedures, ensuring precise tissue sampling from the tumor [37,38].

### Computed tomography (CT)

On CT, SS appears as a hypodense mass compared to adjacent muscle tissue [39,40]. Calcifications are present in approximately 30% of cases, most commonly at the tumor's periphery [36,40]. However, a study by Wilkerson et al. reported that calcifications were present in up to 62.5% of SS cases [41]. The authors themselves acknowledged a limitation of their study—namely, the small sample size (29 participants). In addition to hypodensity and calcifications, contrast enhancement is another critical imaging feature that may indicate the presence of SS. In a retrospective analysis of SS patient cases, Marzano et al. indicated that heterogeneous tumor tissue enhancement is present in up to 90% of cases [42]. Among the less characteristic features of SS, Wang et al. also mention the presence of hemorrhagic and cystic foci [40]. However, these features are not always present, and tumors smaller than 5 cm, with well-defined margins and a relatively slow growth rate, are often misinterpreted as benign lesions [36].

### Magnetic resonance imaging (MRI)

MRI remains the preferred diagnostic method for evaluating soft tissue tumors, including SS. MRI enables high-resolution visualization of the tumor in relation to adjacent structures, allows for precise assessment of local tumor extent, and plays a crucial role in postoperative surveillance [43–45]. SS typically presents as a well-defined, oval or multilobulated mass on MRI. In T1-weighted (T1W) sequences, 50% of cases demonstrate a hypointense signal, while the remaining 50% exhibit an isointense signal relative to adjacent muscle tissue [46]. However, in certain cases, the presence of necrotic tissue or fluid-filled cysts within the tumor may result in hyperintensity in this sequence as well [44]. In relation to T2-weighted (T2W) sequences, Sedaghat et al. reported data indicating that SS consistently appears hyperintense compared to adjacent muscle tissue in all analyzed cases [47]. These findings align with the results of Ashikyan et al., who similarly observed hyperintensity of SS in T2W sequences across all studied cases. Furthermore, among the examined tumors, those containing septations or surrounded by a rim exhibited hypointensity relative to the predominant tumor mass in all cases. Notably, unequivocal results were not observed in T1W sequences. Rim characteristics were hypointense in 71% and hyperintense in 29% of cases, while septation characteristics were hypointense in 78% and hyperintense in 22% of cases [48]. The 'triple sign' is a

characteristic MRI finding of SS, first described by Jones et al. in 1993 [49]. It refers to the simultaneous presence of:

- Hyperintense areas (necrosis, hemorrhagic regions)
- Isointense areas (cellular tumor mass)
- Hypointense areas (calcifications, fibrous tissue)

This finding indicates significant heterogeneity within the tumor. However, it is not pathognomonic for SS [50]. The frequency of this sign in SS has been reported to range from 33% to 50% [39,48,51]. In T2W sequences, homogeneous tumors demonstrate contrast enhancement, with the exception of necrotic foci and fluid-filled spaces, if present, which show no increase in signal intensity following contrast administration [47]. Early arterial enhancement serves as a valuable diagnostic parameter in distinguishing benign lesions from sarcomas. This characteristic is observed in approximately 30% of benign lesions but is present in up to 70% of sarcomas, underscoring its potential utility in the differentiation process [52]. Furthermore, tumor enhancement within <7 seconds after arterial enhancement is a feature consistently observed in cases of SS [53]. This allows differentiating SS from other STS.

### Biopsy

The 2021 ESMO-EURACAN-GENTURIS guidelines recommend multiple core needle biopsies (≥14-16 G needles) as the preferred method for diagnosing STS. Excisional biopsy is advised for superficial lesions located <3 cm from the skin [54]. Accurate histopathological classification relies on immunohistochemistry and molecular testing, particularly the detection of TLE1 and SS18-SSX fusion genes, which are highly specific for SS [55,56]. Fluorescence *in situ* hybridization (FISH) and reverse transcriptase–polymerase chain reaction (RT-PCR) remain the methods of choice for detecting the SS18-SSX mutation in the collected samples [57]. In cases where technical challenges hinder the collection of biopsy samples or where the tumor is located in atypical anatomical regions, ultrasound or CT-guided biopsy proves to be an effective approach. The utility of these techniques largely depends on the operator's expertise, and they offer improved accuracy in tumor sampling [38,58].

*Table 1. Diagnostic methods and their application in SS diagnosis.*

| Modality | Findings in SS | Key Diagnostic Role |
|---|---|---|
| X-ray | Soft tissue mass (67%), calcifications (20%), bony erosion (20%) | Initial screening |
| Ultrasound | id vs. fluid-filled lesion; biopsy guidance | Differentiates cystic from solid masses |
| CT | Hypodense mass, peripheral calcifications (30-62.5%), contrast enhancement | Helps assess extent and calcifications |
| MRI (T1W, T2W) | T1W: Iso-/hypointense; T2W: Hyperintense with "triple sign" (33-50%) | **Gold standard** for local assessment |
| Biopsy | Core needle (≥14-16 G) preferred; SS18-SSX fusion gene | Confirms diagnosis |

## TREATMENT OPTIONS

The therapeutic approach to SS encompasses surgical resection, chemotherapy, and radiotherapy as the primary modalities. In specific clinical scenarios, these methods are integrated into multimodal treatment protocols to enhance patient outcomes [59]. Selecting an appropriate center for the treatment of SS is paramount, and experts emphasize the importance of specialized institutions. These centers should be equipped with a multidisciplinary team, including pediatric/orthopedic surgeons, pathologists, radiologists, and clinical oncologists, all with extensive experience in diagnosing and managing STS. Furthermore, early referral of patients to such specialized centers is critical to optimize outcomes [60,61]. Specifically, any patient with a soft tissue lesion, whether superficial or deep, exceeding 5 cm in diameter, should be promptly referred to a reference center for STS treatment [54].

### Surgery

International guidelines and scientific consensus recommend surgical excision as the treatment of choice for

SS. This approach is particularly considered for patients with localized tumors without the presence of distant metastases [62,63]. According to the 2023 *Consensus on surgical margin definition harmonization from the International Soft Tissue Sarcoma Consortium (INSTRuCT),* the goal of surgery is radical excision with the achievement of microscopically tumor-free margins (R0 resection), while preserving the function and shape of the operated area. The entire excised tumor tissue, including the margin of healthy tissue and the biopsy needle tract, should be removed as one tissue block (en bloc resection) and sent for histopathological examination. In the case of SS adjacent to bone, the surrounding periosteum should be excised. A similar approach applies to tumors near the fascia, where the fascia should also be removed. If the resection is not radical (R1 or R2 margin), reoperation should be performed to excise the scar and the superficial and deep tissues left behind during the initial surgery [64]. In certain anatomical locations, achieving en bloc resection with an R0 margin may be extremely difficult. In these cases preoperative radiotherapy or chemotherapy may be justified to reduce tumor volume and make the surgery more feasible [65,66].

In selected cases, due to the location or advanced stage of the disease, amputation may be the best therapeutic option, allowing for local control and offering the greatest chance of cure. However, this method is generally used as a last resort, for example, in the case of some patients with relapsed SS [62,67]. Metastasis is more frequent in patients undergoing amputation, mainly due to factors like large tumor size and highly malignant histology. However, amputation itself is not an independent risk factor for distant metastasis [68].

In some cases of patients with distant metastases in the lungs, metastasectomy may be considered as a surgical treatment option. However, there is a lack of strong evidence clearly demonstrating a positive impact of this procedure on outcomes [69–71]. This underscores the need for further studies on the impact of metastasectomy on prognosis.

### Radiotherapy (RT)

RT, in combination with surgical resection, represents a cornerstone in the treatment of SS for patients who meet specific eligibility criteria [22]. The ***NCCN Clinical Practice*** *Guidelines in Oncology for Soft Tissue Sarcoma (Version 2.2018)* recommend considering RT for patients with:

- High-grade tumors (G2, G3)
- Unresectable lesions
- R1/R2 surgical margins [72]

Preoperative RT remains essential for tumors larger than 5 cm, recurrent tumors, and those located near critical structures [54,62]. The standard dose for neoadjuvant external beam RT is 50 Gy (1.8-2.0 Gy per fraction), with additional postoperative doses for patients with R1 margins (16-18 Gy**)** and R2 margins **(**20-26 Gy**).** Adjuvant RT uses similar dosing, with patients having R0 margins receiving an additional 10-16 Gy on top of the initial 50 Gy [72]. For patients with regionally advanced disease, RT may be omitted if the postoperative histopathological examination confirms an R0 resection margin, particularly for tumors smaller than 5 cm [15,73]. For patients with distant metastases, the treatment strategy depends on the extent of metastatic disease. Solitary metastases may be managed with a combination of RT, chemotherapy, and metastasectomy. In cases of disseminated metastases, palliative RT should be considered [72]. Previous studies confirm the positive impact of RT on overall survival (OS) among patients with SS [74–76]. Additionally, Song et al. demonstrated a statistically significant improvement in progression-free survival ($p=0.006$) and 5-year local-recurrence-free survival ($p=0.028$) in patients who underwent adjuvant RT after surgery compared to those treated with surgery alone (77). These data highlight RT's significant impact on SS treatment.

## CHEMOTHERAPY

Due to the relatively high sensitivity of SS to chemotherapy compared to other STS, it is often included in treatment strategies, both in the neoadjuvant and adjuvant settings [78]. This results from the high grade of SS cells and its faster growth compared to less chemosensitive, intermediate grade malignant STS, such as schwannomas or leiomyosarcomas[79]. The standard first-line drug is doxorubicin, often combined with ifosfamide [62]. Spurrell et al. showed that this combination treatment is associated with a better response rate (58,6%) compared to doxorubicin alone (25%) or ifosfamide alone (25%) [70]. High-risk patients should be considered for chemotherapy, particularly those with:

- Grade 2 and 3 tumors,
- Primary lesions >5 cm,
- R1 and R2 resection,
- Selected cases of R0 resection

- Presence of metastases [54,73].

Scientific evidence on the impact of chemotherapy on the prognosis of adult patients with SS remains conflicting, indicating that it should be used only in specific cases [22,80–83]. Currently, pazopanib, a tyrosine kinase inhibitor, remains the only drug beyond classical chemotherapeutics used in patients with SS (84). Ongoing research focuses on developing new drugs, particularly immunotherapy, to improve prognosis and reduce side effects of conventional therapies in SS patients [85–88].

# PROGNOSIS

## PATIENT-SPECIFIC FACTORS

The prognosis among patients with SS is variable and depends on a combination of patient-specific factors and tumor-related characteristics. An analysis of the SEER database conducted by Aytekin et al. revealed that among patients with SS, the one-, five-, ten-, and twenty-year survival rates were 87.3%, 59.4%, 50.8%, and 42.8%, respectively, with a median OS of 138 months. However, age-based subgroup analysis showed a significant difference in survival. Among patients aged ≥35 years, median OS was only 60 months, which was statistically significantly lower than the 200 months observed in patients under 35 years of age ($p<0.001$) [89]. These data confirm that age ≥35 years of age is an independent prognostic factor for unfavorable outcome in patients with SS. The better prognosis in younger patients is confirmed by Vlenterie et al., who found the highest OS rate in those under 18 years of age [90]. Male gender and Black race are additional factors associated with a worse prognosis [75]. However, the authors do not explain the underlying mechanisms of this poorer outcome in these patient groups. Interestingly, Sultan et al. observed that these factors did not significantly affect prognosis in the pediatric population. However, the authors themselves acknowledge that these findings may be influenced by the relatively small number of children included in the study [91]. A particularly unfavorable prognostic factor is the presence of distant metastases at the time of diagnosis [33]. Smolle et al. demonstrated that in this patient group, the 5-year cancer-specific survival is 22.6% [92]. This represents a nearly threefold worse outcome compared to patients without distant metastases.

## TUMOR CHARACTERISTICS

Tumor-related prognostic features include the size of the primary lesion, histological subtype, tumor grade and negative surgical margins. For STS, a tumor size of 5 cm serves as the threshold for classifying a lesion as T1 according to the TNM classification. Tumors larger than this diameter are categorized as T2 or higher [93]. Kang et al. demonstrated that in cases of STS, a tumor size exceeding 5 cm is associated with a worse prognosis compared to smaller lesions. The disease-specific survival at 5 years was 87.4% in the T1 group versus 74.9% in the T2 group ($p=0.001$) (94). Research on SS indicates that, like other STS, larger tumor size at diagnosis is associated with a worse prognosis [92,95–97]. The histological subtype of the tumor is a significant factor in assessing prognosis. Studies indicate that the biphasic subtype has the most favorable outcomes among all histological variants of SS. Conversely, the epithelioid subtype is associated with the poorest OS [13,89]. These findings are corroborated by a study by Xiong et al., which analyzed 1692 patients and demonstrated that the five- and ten-year survival rates varied by histological subtype: biphasic subtype (69%, 60%), monophasic subtype (59%, 49%), and epithelioid subtype (32%, 26%) [11]. These data confirm the superior prognosis for the biphasic SS subtype compared to other variants. Fice et al. also highlighted the significant impact of histological grade on prognosis, reporting an metastasis-free survival (MFS) rate of 86,5% for G2 tumors, while G3 tumors had a markedly lower MFS rate of just 50% ($p=0,026$) [98]. The negative impact of higher histological grades on MFS has also been confirmed by Trassard et al. [99].

## RADICALITY OF SURGERY

The radicality of surgical resection is another significant factor influencing prognosis. Numerous studies have shown that incomplete resection (R1/R2) significantly worsens overall survival [22,32,100]. The impact of this factor on the occurrence of distant metastases in the future varies depending on the source, with Sacchetti et al. demonstrating, after performing a multivariate analysis, that its effect is just above statistical significance, despite showing a significant influence on recurrence-free survival in univariate analyses [77,100,101]. A multicenter study by Trovik et al. involving 559 patients and a systematic review by Fanfan et al. including 123 patients found no significant impact of resection radicality on the development of distant metastases [102,103]. These studies did not differentiate between STS types, highlighting the need for a meta-analysis focused on the impact of resection on distant metastasis development in SS patients. Incomplete resection also negatively affects local recurrence outcomes [104]. These findings emphasize the critical role of achieving an R0 margin in resection for prognosis.

# CONCLUSION

1. Synovial sarcoma (SS) presents a significant clinical challenge due to its high aggressiveness, complex diagnosis, and limited therapeutic options. Early diagnosis and referral of patients to specialized centers with multidisciplinary teams are key factors for successful treatment.
2. Surgical treatment remains the primary therapeutic approach for SS. Achieving an R0 resection (microscopically tumor-free margins) is critical for improving overall survival and reducing the risk of local recurrence. In cases where radical surgery is not feasible, neoadjuvant chemotherapy and/or radiotherapy may be justified.
3. Radiotherapy is an essential component of combined treatment, particularly for patients with high-grade tumors, positive surgical margins (R1/R2), and large tumors (>5 cm). It contributes to reducing the risk of local recurrence and improving overall survival.
4. Chemotherapy is used in neoadjuvant or adjuvant settings, especially for high-risk patients (G2-G3 tumors, >5 cm, R1/R2 resection, metastases). However, its impact on long-term survival remains controversial, and treatment decisions should be individualized.
5. The prognosis of SS depends on multiple factors, including patient age, tumor size, histological subtype, tumor grade, and the radicality of surgical intervention. Younger patients (<35 years) have significantly better overall survival rates, whereas the presence of distant metastases at diagnosis drastically worsens the prognosis.
6. Targeted therapy and immunotherapy represent promising directions in SS treatment, with the potential to revolutionize management, particularly for patients with advanced and treatment-resistant forms of the disease. Further research is necessary to develop more effective treatment strategies.
7. The key to successful SS treatment is early diagnosis and a comprehensive therapeutic approach. Patients should be treated in specialized centers with the necessary expertise and resources. The development of personalized treatment strategies based on molecular tumor profiling remains a crucial goal in modern oncology.

## DISCLOSURES

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