Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 26; 10(B):1426-1431.
https://doi.org/10.3889/oamjms.2022.9770
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Oncology*

Epidemiological Trend Analysis and Survival Data of Balinese with Soft-Tissue Sarcoma in 2015–2021

I. Wayan Sudarsa[1]*, Citra Aryanti[2]

[1]Department of Surgery, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia; [2]Department of Surgery, Division of Surgical Oncology, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Sudarsa IW, Aryanti C. Epidemiological Trend Analysis and Survival Data of Balinese with Soft-Tissue Sarcoma in 2015–2021. Open Access Maced J Med Sci. 2022 May 26; 10(B):1426-1431. https://doi.org/10.3889/oamjms.2022.9770
Keywords: Soft-tissue sarcoma; Incidence; Mortality; Survival; Subtype
***Correspondence:** Citra Aryanti, Department of Surgery, Udayana University, Sanglah General Hospital, Jl. Kesehatan No. 1, Denpasar, Bali, Indonesia. E-mail: citra.aryanti@hotmail.com
Received: 12-Apr-2022
Revised: 26-Apr-2022
Accepted: 16-May-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Soft-tissue sarcoma (STS) has a very heterogen features of its nature, subtypes, and clinical behavior among population. Regardless, the epidemiology data of STS are very limited in developing countries, including Indonesia.

AIM: The aim of this study was to describe the incidence and mortality trend analysis, as long as the survival data in Bali from 2015 to 2020.

METHODS: This is a case–control study including all subjects with STS in Denpasar, Bali, Indonesia from January 2015 to September 2021. Data about demographics, clinical, and survival timing data were collected from Cancer Registry. STS diagnosis was confirmed after histopathological examination. Joinpoint regression was used for crude rate trend analysis. Data were analyzed by SPSS 22.0, using Kaplan–Meier for survival analysis.

RESULTS: Ninety-three subjects with STS were included in this study. Most patients died at the end of the study (65.6%) with median survival of only 30 months. The trend of STS age-standardized incidence and mortality rate was increasing from 2015 to 2018, then declining until 2020. The survival rate varies among the STS subtypes and location. It was better in the group without metastases, underwent therapy, but not statistically significant.

CONCLUSION: STS showed a diversity of demographic and clinical parameters. The incidence and mortality rate has plateaued in 2018, but then declining. The survival rate diversed regarding of the STS subtype, location, metastasis, and treatment given.

Introduction

Soft-tissue sarcoma (STS), tumors that develop from mesenchymal cells, accounts for <1% of cancers worldwide. This type of cancer continues to be studied due to its varied nature, increasing incidence, but no optimal treatment has been found [1]. Demographic, clinical, and STS survival data vary widely from those published in various regions [2].

Each STS subtype had a completely different prognosis due to its heterogeneity. The complexity of STS makes it challenging to study as well as its management [3]. Research and data on STS are very limited in developing countries, especially Indonesia. To obtain the accurate population-based data of sarcoma, this study will take a broad perspective from the epidemiology of sarcoma, focusing on incidence and mortality trend analysis, as long as the survival data in Bali from 2015 to 2020.

Materials and Methods

Design and population of the study

All patients with STS who visited the Division of Oncology Surgery, Department of Surgery, Denpasar, Bali, Indonesia from January 2015 to September 2021 were collected, including 93 patients. All patients were included in this retrospective study. The study was approved by the Ethical Committee Faculty of Medicine Udayana University, and informed consent was acquired from each participant.

Data sources

STS cases diagnosed during 2015–2021 were obtained from the Bali's Cancer Registry, maintained by the Division of Oncology Surgery, Department of Surgery, Denpasar, Bali, Indonesia. In this study, only STS data were included in the

study. We exclude the bone sarcoma and the STS in gastrointestinal tract.

The registry includes cancer information from all districts in Bali, Indonesia. Demographic, histopathology, and treatment data were available for each case. Any missing data were obtained by calling the registered phone number, and electronic medical records of the hospital. Data of the total Bali population were obtained from the Population Statistic Center of Bali.

Data collection

Data were obtained retrospectively from patients' medical records. The demographic variables collected were age at diagnosis, gender, ethnicity, marital status, highest education level, location of residence, and employment. The clinical variables collected were tumor size at diagnosis, tumor location, history of treatment (surgery, chemotherapy, and radiotherapy), disease progression (residive and recurrent), metastasis status, subtype of STS, and survival data. In this study, we also collected the delay timing from onset to treatment seeking, the timing from treatment to mortality, and the timing from onset to mortality.

The age at diagnosis was determined at the 1st time the patient visited our institution. For ethnicity, we classified as Balinese, Javanese, and others, based on the majority ethnicity in our population. The tumor size at diagnosis measured by the largest diameter of tumor at the initial presentation. Tumor location was classified as head-neck, oral (including maxilla, mandibula, and gum), trunk, upper arm, lower arm, upper leg, and lower leg.

The STS diagnosis was confirmed after subsequent histolopathology examination by a dedicated sarcoma pathologist. All histopathological findings were obtained from biopsy or surgically resected specimens from files of patients. The subtype of STS was classified based on the latest 2020 WHO classification of STS. The main treatment for patients at our institution is surgery, either wide excision or amputation. The adjuvant therapy was adjuvant chemotherapy. After that, the patient was registered for external radiotherapy with the radiation dose determined by the radiation oncologist.

All patients received follow-up from the date of diagnosis until they died or until the last date of the study in August 2021. Follow-up visits were scheduled every month for the first 6 months and every 6 months after completion of therapy unless any non-scheduled visit was indicated. The follow-up included clinical examination, abdominal ultrasonography, chest X-ray, and bone survey.

Local recurrence was described as the first recurrence of disease at the primary tumor site detected clinically, while the residive status was given if the tumor arised again in the same location with the history of the previous surgical margin still contained cancer cells. The status of metastasis was obtained from the presence of the same tumor cells at the distant organ, which found in scheduled follow-up visits. The survival time was determined by the duration from the first initial tumor onset until the death or the last date of the study (censored).

Statistical analysis

The statistical analyses above were carried out using the Statistical Package for the Social Science software version 22.0 (SPSS Inc.). Numeric variables were described as median and mean with standard deviation. Trend analysis was plotted using the chart in the Microsoft Excel and annual percentage change was determined using crude rate in joinpoint regression program. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals were calculated by Cox proportional hazard models. $p < 0.05$ was considered significant.

Results

Demographic and clinicopathological characteristics

Of the total 93 subjects, the median age at diagnosis was 49 years old, and the mean age at diagnosis was 48.61 years old. The majority of patients were male (55.9%), balinese (75.3%), married (88.2%), junior high school graduates or lower education level (52.7%), living in the rural area (69.9%), and farmer (34.5%). The median tumor size of diagnosis was 10 cm, which occurred mainly in the trunk (19.2%). Of those, 31.2% had metastasis, majority with lung metastasis. Around 65.6% of patients underwent surgery, either wide excision or amputation. Only 28% patients received chemotherapy and 20.4% of patient received radiotherapy. Most patients died at the end of the study (65.6%) with median survival of only 30 months (Table 1).

Trend of STS annual incidence and mortality rate

Trend analysis was performed from 2015 to 2020. The mortality trend of STS also showed the same pattern. The age standardized incidence rate (ASIR) of STS in Bali is shown in Figure 1. The highest ASIR was in 2018 (ASIR 1.157), then decline afterward. The annual percentage decrease change from 2017 to 2018 was 69.2% and the annual percentage increase change

Table 1: Demographic and clinical variables of soft-tissue sarcoma patients

Variables	n (%)
Age at diagnosis	
Median	49
Mean	48.61 ± 15.36
Gender	
Male	52 (55.9)
Female	41 (44.1)
Ethnicity	
Balinese	70 (75.3)
Javanese	15 (16.1)
Others	8 (8.6)
Marital status	
Married	82 (88.2)
Not married	11 (11.8)
Highest education level	
Junior high school or lower education level	49 (52.7)
Senior high school	35 (37.6)
University	6 (6.5)
Residence	
Rural	65 (69.9)
Urban	28 (30.1
Employment	
Unemployed	25 (26.9)
Farmer	32 (34.5)
Employee	18 (19.3)
Private	18 (19.3)
Tumor size at diagnosis	
Median	10
Mean	11.15 ± 6.97
Time delay to initial treatment	
Median	12
Mean	16.94 ± 14.96
Location	
Head-neck	4 (0.3)
Oral	9 (9.7)
Trunk	17 (19.2)
Upper arm	12 (12.9)
Lower arm	8 (8.6)
Upper leg	31 (33.3)
Lower leg	12 (12.0)
Surgery	
Yes	61 (65.6)
No	32 (34.4)
Chemotherapy	
Yes	26 (28)
No	67 (72)
Radiotherapy	
Yes	19 (20.4)
No	74 (79.6)
Disease progression	
Residive	18 (19.4)
Recurrent	13 (13.9)
No residual or recurrent case	62 (66.7)
Metastasis	
Yes	29 (31.2)
Lung	21 (22.5)
Bone	2 (2.2)
Brain	1 (1.1)
More than one organ	5 (5.4)
No	64 (68.8)
Status	
Survived	32 (34.4)
Died	61 (65.6)
Subtype	
Adipocytic tumors	
Dedifferentiated liposarcoma	1 (1.2)
Myxoid liposarcoma	6 (7.2)
Pleomorphic liposarcoma	3 (3.6)
Liposarcoma, not otherwise specified	1 (1.2)
Fibroblastic/myofibroblastic tumors	
Low-grade myofibroblastic sarcoma	5 (6.0)
Dermatofibrosarcoma protuberans	5 (6.0)
Adult fibrosarcoma	7 (8.4)
Myxofibrosarcoma	10 (12.0)
Smooth muscle tumors	
Leiomyosarcoma	2 (2.4)
Skeletal-muscle tumors	
Alveolar rhabdomyosarcoma	4 (4.8)
Pleomorphic rhabdomyosarcoma	9 (10.8)
Nerve sheath tumors	
Malignant peripheral nerve sheath tumor	12 (14.5)
Tumors of uncertain differentiation	
Synovial sarcoma NOS	2 (2.4)
Epithelioid sarcoma	1 (1.2)
Extraskeletal myxoid chondrosarcoma	3 (3.6)
Desmoplastic small round cell tumor	1 (1.2)
Extrarenal rhabdoid tumor	1 (1.2)
Undifferentiated sarcomas	
Undifferentiated spindle cell sarcoma	2 (2.4)
Undifferentiated pleomorphic sarcoma	13 (15.7)
Undifferentiated round cell sarcoma	5 (6.0)

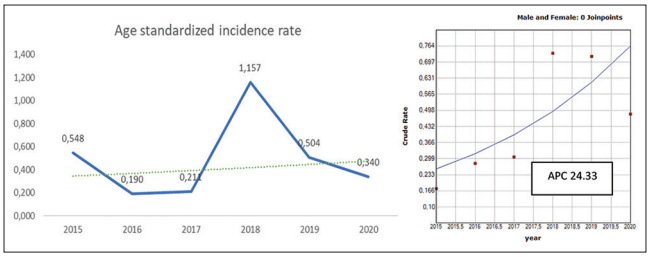

Figure 1: Trends in the annual incidence rate of soft-tissue sarcoma patients in Bali over the period of 2015–2020

from 2018 to 2019 was 39.3%. The crude incidence rate trend analysis using joinpoint regression showed that the annual percentage change was 24.33.

The trend of STS mortality was increasing from 2015 to 2018, then declining until 2020. The age standardized mortality rate (ASMR) of STS in Bali is shown in Figure 2. The highest ASMR was in 2018 (ASMR 0.919), then decline afterward. The annual percentage decrease change from 2017 to 2018 was 66% and the annual percentage increase change from 2018 to 2019 was 45.5%. The crude incidence rate trend analysis using joinpoint regression showed that the annual percentage change was 15.01.

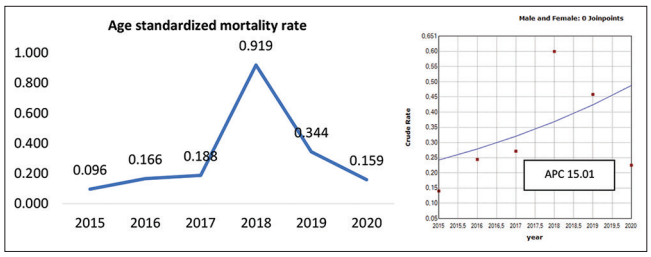

Figure 2: Trends in the annual mortality rate of soft-tissue sarcoma patients in Bali over the period of 2015–2020

Duration of survival based on the STS subtypes

In this study, there were 20 subtypes of STS identified based on the histopathological examination. The most common types of STS were undifferentiated pleomorphic sarcoma (15.7%) and malignant peripheral nerve sheath tumor (14.5%). From the Mantel-Cox log-rank analysis, there was no significant difference between STS subtypes and mortality (p = 0.467). STS subtypes with the shortest survival time even after therapy was pleomorphic liposarcoma. STS subtypes that have the longest survival time after therapy was extraskeletal myxoid chondrosarcoma. STS subtype with the longest survival time from onset to death regardless of the therapy status was undifferentiated spindle cell sarcoma. STS subtype with the shortest survival time from onset to death regardless of the therapy status was undifferentiated round cell sarcoma (Figure 3).

Survival analysis based on the location, metastasis status, and treatment

Cumulative survival curves as a function of time were generated using the Kaplan–Meier approach and compared using a log-rank test. The location of the STS with the lowest duration of survival was in the head neck (8 months median survival, HR 1.95, 95% CI 0.507–0.7458). However, there was no difference in mortality between each STS site (p = 0.582) (Figure 4a). The median survival time for

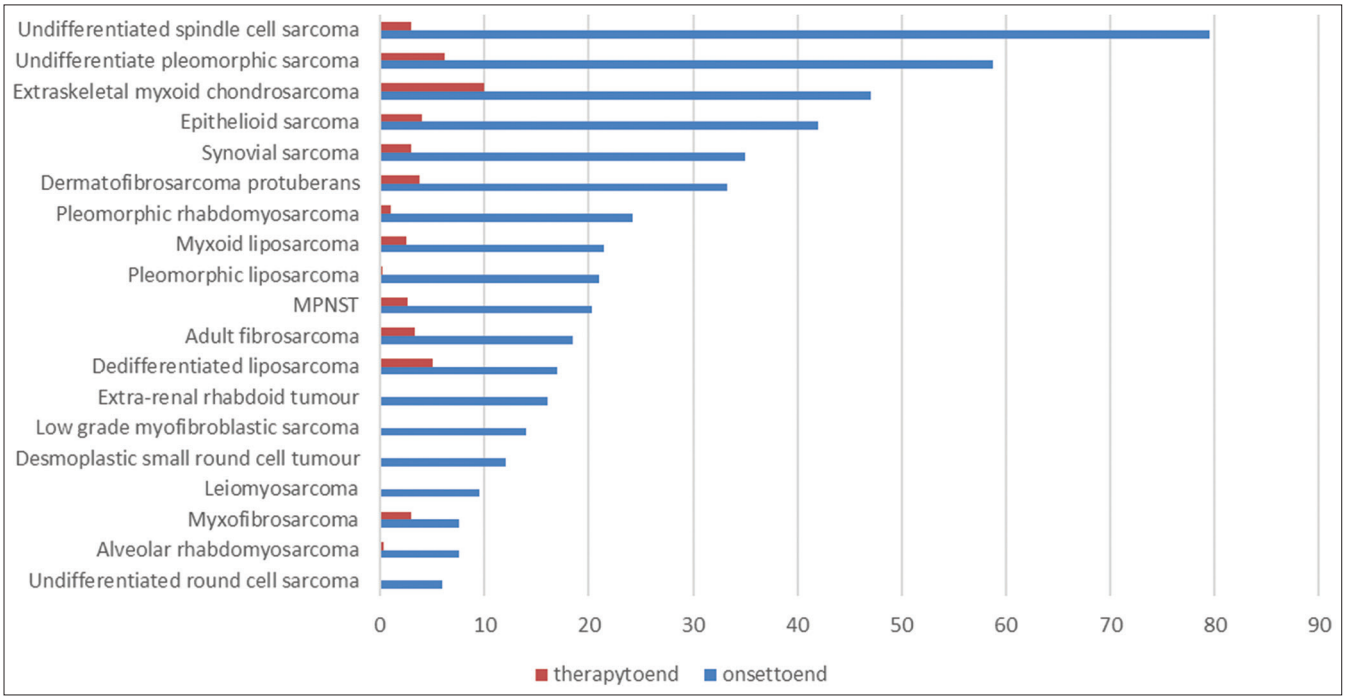

Figure 3: The survival duration of each subtype of soft-tissue sarcoma. The blue-colored bars indicate the duration of survival time from onset to death, while the orange colored bars indicate the duration of survival time from therapy to death

patients with metastases was lower than for patients without metastases, although not significant (29 versus 37 months, respectively, HR 1,114, 95% CI 0.659–1.885, p = 0.686). Subjects with metastases to organs other than the lung had a better median survival than those with lung metastases alone (30 vs. 17 months, respectively) (Figure 4b). The median survival time of patients who underwent therapy was higher than that of patients who did not receive treatment (40 vs. 14 months, HR 1.67, 95% CI 0.89–3.131, p = 0.204). No survival advantages if comparing of all treatment modalities (Figure 4c).

Discussion

STS has more than 50 molecular subtypes, with each subtype displaying variable clinical behavior. Its heterogeneity made this cancer challenging to understand and to treat. In this study, only 93 cases were found from 2015 to 2021. The incidence rate also lower than reported in another country. The author believes that many cases were not detected or even died when they arrived at the hospital. Almost all cases of STS treated in Bali are in an advanced stage.

In this study, the median age of patients treated with STS was 49 years and mostly male and farmer [4]. This is consistent with the prevalence of STS in the global population with male dominance and diagnosed in the fifth decade of life. In the USA, the most common histology was non-special type sarcoma (14.8%), sized over 5 cm, and had distant metastasis (75.8%) at diagnosis [5]. In Europe, the most frequent morphology was leiomyosarcoma (20%) with mean size 10 cm [6]. In Asia, the systematic review of Ngan *et al*. (2013), the most commonly reported STS subtype was pleomorphic sarcoma, mostly happened in male, and aged 26–61 years old [7]. In Indonesia, only one published study about epidemiology of sarcoma. Arfiana (2013) showed that during 2009–2013, there were 195 cases of STS, mostly found in female (60%), aged 40–49 years old, and most commonly subtype was rhabdomyosarcoma (17.9%). However, the study included both pediatric and adult populations [8].

The location of STS was very heterogeneous, depending on the subtypes. Somehow, each study showed different predilection. Clark *et al*. (2005) which considered only adult soft-tissue cases reported that 40% arose on a lower limb [9]. A 2015 survey of STS s in France showed that 49% found at limb (include four limb) and 40% in truncal [10]. In this study, most cases were found in the trunks.

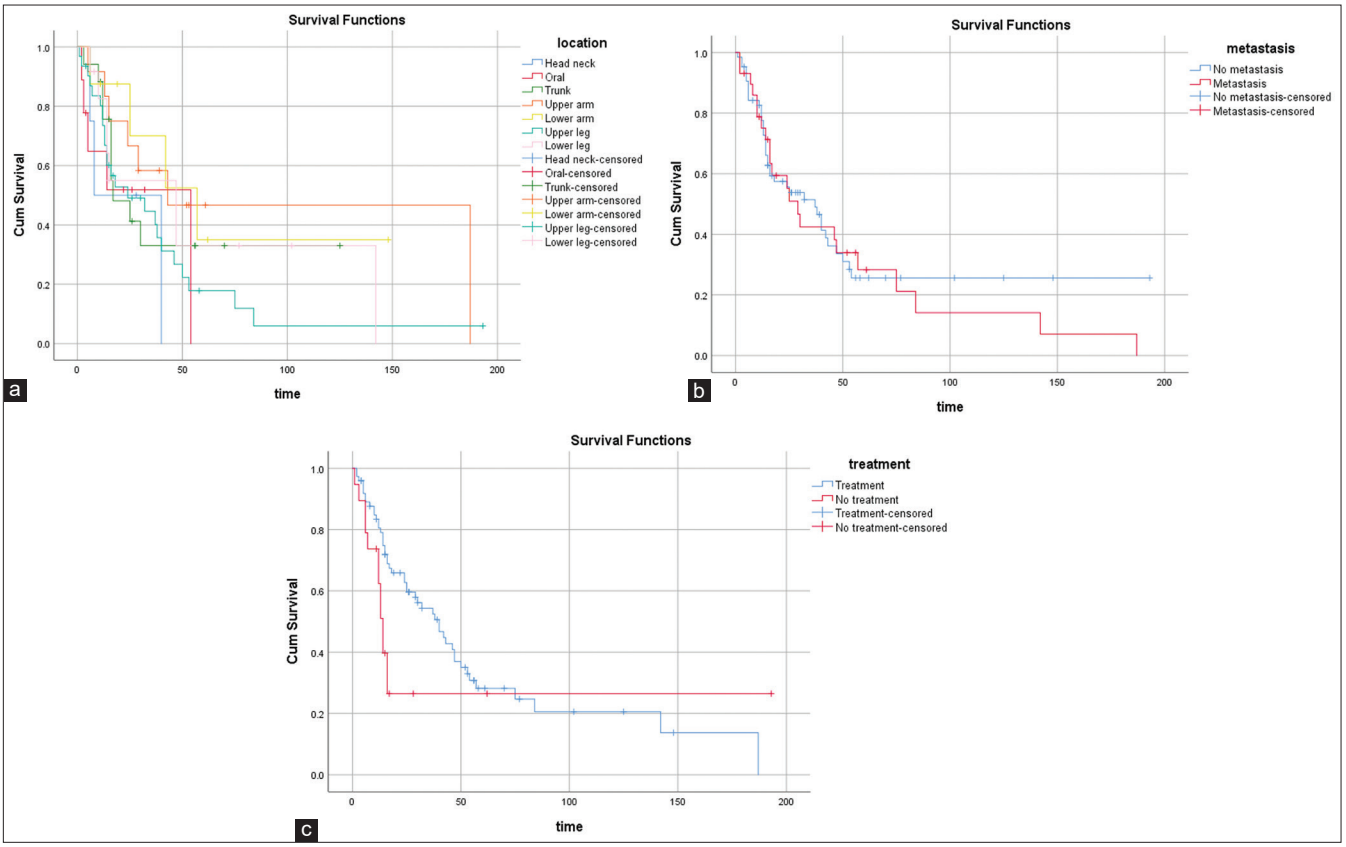

Figure 4: Kaplan–Meier survival curves with log-rank test according to (a) location, (b) metastasis status, and (c) treatment status

The standard primary treatment for STS is surgical resection, with appropriate negative margins where possible, followed by systemic therapy (such as chemotherapy, targeted therapy, immunotherapy, and radiotherapy) [11]. In this study, most of the patients underwent surgery (either wide excision or amputation), however not a few have non-tumor-free margins. Even those with tumor-free margins also showed high residive, recurrence, and progression rates. From our observation, the administration of standardized adjuvant VAC chemotherapy and radiotherapy was controversial and in some patients, there was no benefit found. In Asia, nearly all patients (98%) treated with surgery, followed by adjuvant radiotherapy or chemotherapy. Survival outcomes and recurrence rates varied among the studies due to the different histotypes, sites, and disease stages assessed [7].

The survival of STS even with various therapies was still not satisfactory. In the USA, the 1, 5, and 10-year survival were 87%, 71%, and 66%, respectively. However, this project included all types of sarcoma, including GI tract STS and bone sarcoma. In Europe, 5-year relative survival from STS was 54% in Eastern Europe and the UK and Ireland and 60% in the other three European regions [6]. Median overall survival of 11 months was shown in patients who presented with metastatic STS [12].

This study took a complete data from the tertiary hospital in Bali, in which STS cases will be referred to this institution. All patients with STS were included in this study. In future study, advanced epidemiological data utilized in gathering exposure information must also be considered. A registry system might seem not enough, so population-based study may allow for highly accurate exposure information. Incorporating molecular genetic evaluation will be valuable in future study and make a great contribution for tumorigenesis understand and a key point for its management.

Conclusion

STS showed a diversity of demographic and clinical parameters. The incidence and mortality rate has plateaued in 2018, but then declining. The survival rate diversed regarding of the STS subtype, location, metastasis, and treatment given.

Acknowledgment

The authors acknowledge the Division of Surgical Oncology, Department of Surgery, Denpasar, Bali, Indonesia, which has given a robust support for this study.

Data Availability

The data used in this paper are available from the corresponding author on reasonable request.

References

1. Naing KW, Monjazeb AM, Li CS, Lee LY, Yang A, Borys D, *et al*. Perioperative radiotherapy is associated with improved survival among patients with synovial sarcoma: A SEER analysis. J Surg Oncol. 2015;111(2):158-64. https://doi.org/10.1002/jso.23780
   PMid:25176165
2. Jacobs AJ, Morris CD, Levin AS. Synovial sarcoma is not associated with a higher risk of lymph node metastasis compared with other soft tissue sarcomas. Clin Orthop Relat Res. 2018;476(3):589-598. https://doi.org/10.1007/s11999.0000000000000057
   PMid:29529647
3. Vodanovich DA, Choong PF. Soft-tissue sarcomas. Indian J Orthop. 2018;52(1):35-44. https://doi.org/10.4103/ortho.IJOrtho_220_17
   PMid:29416168
4. Edwards D, Voronina A, Attwood K, Grand'Maison A. Association between occupational exposures and sarcoma incidence and mortality: Systematic review and meta-analysis. Syst Rev. 2021;10(1):231-9. https://doi.org/10.1186/s13643-021-01769-4
5. Gage MM, Nagarajan N, Ruck JM, Canner JK, Khan S, Giuliano K, *et al*. Sarcomas in the United States: Recent trends and a call for improved staging. Oncotarget. 2019;10(25):2462-74. https://doi.org/10.18632/oncotarget.26809
   PMid:31069009
6. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, *et al*. Descriptive epidemiology of sarcomas in Europe: Report from the RARECARE project. Eur J Cancer. 2013;49(3):684-95. https://doi.org/10.1016/j.ejca.2012.09.011
   PMid:23079473
7. Ngan R, Wang E, Porter D, Desai J, Prayogo N, Devi B, *et al*. Soft-tissue sarcomas in the Asia-Pacific region: A systematic review. Asian Pac J Cancer Prev. 2013;14(11):6821-32. https://doi.org/10.7314/apjcp.2013.14.11.6821
   PMid:24377612
8. Arfiana W, Burhanudidn L, Fidiawati WA. The distribution of soft tissue sarcoma based on histopathology's check-in Pekanbaru's Hospital between 2009-2013. Jom FK. 2016;3(1):1-9.
9. Clark MA, Fischer C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005;353(7):701-11. https://doi.org/10.1056/NEJMra041866
   PMid:16107623
10. Honoré C, Méeus P, Stoeckle E, Bonvalot S. Soft tissue sarcoma in France in 2015: Epidemiology, classification and organization of clinical care. J Visc Surg. 2015;152(4):223-30. https://doi.org/10.1016/j.jviscsurg.2015.05.001
    PMid:26088366
11. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma. 2010;2010:506182. https://doi.org/10.1155/2010/506182
    PMid:20634933
12. Quek RH, Farid M, Wang E, Asavamongkolkul AM, Leung A, Prayogo N, *et al*. Epidemiology, treatment (tx) patterns and outcomes in Asian soft tissue sarcoma (STS) patients: Results from the Soft Tissue Sarcoma in the Asia Pacific Region (STAR) study. J Clin Oncol. 2015;33(15):10549.