EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 8
318-323
Year: 2020

SURGICAL IMPLICATIONS ON SYNOVIAL SARCOMA

Ratheesh R. Asokan[1], Manroop Sahota[2], Olivia Dix[3], Muhammad Ismail Khan[4] and Mala Thakur*[5]

Medicine, Xavier University School of Medicine, Oranjestad, ABW.

***Corresponding Author: Mala Thakur**
Medicine, Xavier University School of Medicine, Oranjestad, ABW.

Article Received on 02/06/2020 **Article Revised on 02/07/2020** **Article Accepted on 22/07/2020**

ABSTRACT
Each year 1 to 3 million individuals are diagnosed with the rare and aggressive soft tissue cancer, synovial sarcomas. Affecting young adults between the ages of 15 and 35, this rare yet malignant cancer, has the ability to occur anywhere throughout the body. Although the name itself states synovial as the possible origin, it actually originates from the multipotent stem cells and differentiate into mesenchymal cells. In this study, we review surgical implications that occur on synovial sarcomas and provide an overview of synovial sarcoma, components of the tumor, as well as a glance at its future.

KEYWORDS: Synovial sarcoma.

I. INTRODUCTION

Sarcomas are malignant cancers of the embryonic connective tissue.[1] This tumor is predominately found in the soft tissue of juxta-articular structures; Such as, around the knee, at the shoulder, arm, elbow, and the wrist. The most common sarcoma of soft tissue is in the foot. The nature of this tumor reveals aggressive local behavior, which allows for it to metastasize. Synovial sarcoma is defined as the fourth most common type of sarcoma, affecting adults between the ages of 15 and 35. Also, it is seen to affect males more than females.[2] Synovial sarcoma presents with chromosomal translocation, affected patients will have either, or both, SS18 (SYT) gene on chromosome 18 and either SSX1 or SSX2 gene on their chromosome X.[3] Different types of synovial sarcoma's include: Ewing's sarcoma, and myxoid liposarcoma.[1] Ewing's sarcoma is a rapid growth tumor that accompanies little to no pain. This tumor is seen to affect individuals between ages 10 and 30 and is usually located in deep muscle areas in the lower extremity.[2] Myxoid liposarcoma is the second most common type of liposarcoma, that affects young adults and children. This tumor presents in deep soft tissues of the extremities, as a large mass. The mass is painless, and most of the abnormal tissue growth can be found on the thigh.[4] The use of surgery, conservation therapy, and radiotherapy are utilized to control synovial sarcoma. However, the rate of death from the disease stays sizable. No further advancements have come forward, concerning better outcomes for patients with the tumor.[5]

a. Histology

Synovial sarcoma is one of the most common soft tissue malignancies in young and middle-aged adults likely seen in extremities.[6] It was shown that synovial sarcoma is 10% of all types of sarcomas.[7] Synovial sarcoma is known to be at a high grade due to its histological and morphological spectrum is wide causing a decrease in distinguishing identifiers.[6] Synovial sarcoma in the lungs is an aggressive tumor sharing histologic features with other soft tissue sarcomas.[8] This similarity can cause diagnosis very difficult when presented with a case in synovial sarcoma.

Synovial sarcomas can be classified into 3 types of histological variants, monophasic, biphasic, and poorly differentiated or round cells.[7] Diagnosing these types of cancers may become difficult due to indistinguishable histological features between synovial sarcoma and other soft tissue tumors. Biphasic synovial sarcoma is usually distinctive with its histology; however, monophasic synovial sarcoma becomes poorly differentiated and can be sought to be other types of cancers like spindle cell tumors.[7] Synovial sarcoma was said to be biphasic tumors containing epithelial and uniform spindle cell components.[9] Synovial sarcoma can histologically appear spindle-shaped with gland-like epithelial cells and synovial lining cells.[10] Poorly differentiated synovial sarcoma appears to be more like round cells.[11] However, with greater exploration scientists realized that synovial sarcoma is much more developed than that. It was described with wider morphological spectrums including monophasic spindle cell and poorly differentiated subtypes and the biphasic subtypes are seemed to be a minority of the cases of synovial sarcoma.[9]

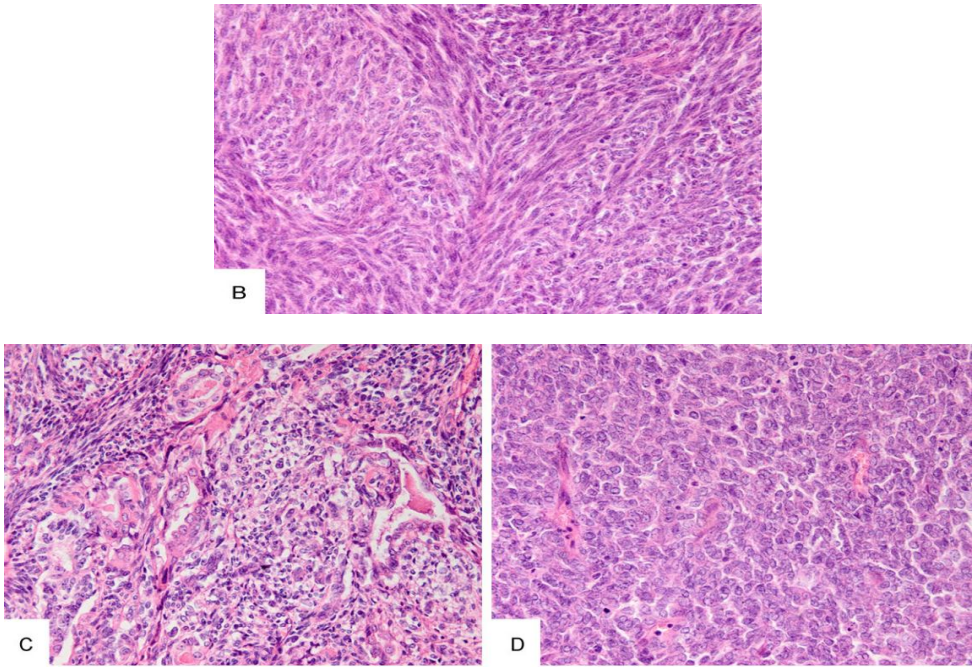


Figure 1. B. Monophasic synovial sarcoma. C. Biphasic synovial sarcoma. D. Poorly differentiated synovial sarcoma (original magnification 400×).[11]

Since histological variants are not identifiable of synovial sarcoma, immunohistochemical could help with diagnosis each tumor. Some common markers that may help with the diagnosis are cytokeratin's, epithelial membrane antigen, and BCL-2.[7] Most of these immunohistochemical markers are not sensitive to synovial sarcoma, which decreasing the accuracy of the diagnosis.[7] Makers like S-100 protein and CD99 are also commonly seen in synovial sarcoma that can be used to distinguish between other cancers.[7] Cases of synovial sarcoma showed a focally strong association with S100 staining with overlapping neurofilament staining.[9] This aroused that synovial sarcoma was not coming from peripheral nerves but axons running through the tumor caused the strong positive marker for S100.[9] S-100 markers can be shown in multiple tumors like synovial sarcoma and peripheral sheath tumors so it's not a distinguishing marker to diagnosis synovial sarcoma.[8] However, in primary pulmonary synovial sarcoma, there are often other markers that can be seen, such as cytokeratin 7.[8] This factor can then distinguish between these two malignancies. In recent studies, gene expression is commonly seen as a marker for histological features to identify pathologies. One specifically for synovial sarcoma is the TLE gene, which is shown to be overexpressed in synovial sarcoma.[7] This could lead to a potential marker for this soft tumor. It also has histological features to identify synovial sarcoma from other types of malignancies. Test diagnostics can be utilized for antibodies against specific proteins and expressed genes to identify the specific tumors.[9] With the antibody-protein combination, specific staining can be assessed to identify the immunohistochemical markers of synovial sarcoma.[9] The type of expression these tumors need is extensive tests including DNA expression profiling. There are specific genes that are characteristically seen in synovial sarcoma.[9] These immunohistochemistry tests confirm to distinguish synovial sarcoma from other types of soft tumors.[9] EGFR is detected in synovial sarcoma on antibody 31G7 which shows 38% of synovial sarcoma in immunostaining.[9] Although EGFR may be a potential marker for synovial sarcoma, it was more possible as a therapeutic target for research and treatment teams by the response of EGFR inhibitors in synovial sarcomas.[9] EGFR may define tumors by providing specific agents allowing them to treat the synovial sarcoma at the beginning.[9]

cDNA microarray analysis shows a higher correlation in synovial sarcoma due to it being expressed in 50% of all synovial sarcomas.[9] In both cDNA and EGFR, associated genes have strong staining for synovial sarcoma when compared to other soft tumors.[9] cDNA expression provides a practical confirmatory test for specific proteins being expressed in these types of tumors which can also be applied to clinical diagnosis.[9] This could also lead to more localization of tumor cells as well.[9] This provides an overall confirmation between diagnosis in the clinic and a specific test to localize the tumor. Synovial sarcoma is still very hard to the differential between some soft malignancies due to the undefined borders of the tumor. Unknown tumors can be tested for classes basic immunohistochemical profiles like synovial sarcoma has many different correlations between markers.[9] A definite diagnosis may need multiple panels of markers to make sure the answer is synovial sarcoma which can be extensive.[9] Overall, synovial sarcoma is a difficult diagnosis that needs multiple angles to understand the histological findings of this type of soft tumor.

a. Monophasic and biphasic synovial sarcoma

Synovial sarcoma can either be characterized by its resulting tumors which can be divided into three subtypes: monophasic(pure sarcomas), biphasic, or poorly differentiated tumors.[12] Biphasic synovial sarcoma types contain spindle cell elements and epithelial elements that occur in various proportions. Monophasic type contains only uniform spindle cells(monophasic fibrous) or epithelial cells(monophasic epithelioid).[13]

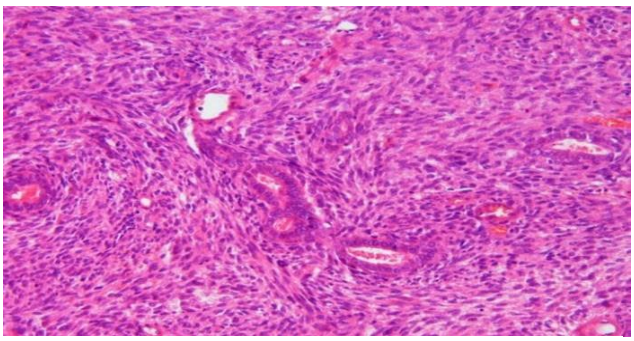
Nearly most monophasic synovial sarcomas carry an SYTSSX2 fusion, as opposed to the classic biphasic synovial sarcomas that carry an SYT-SSX1 fusion.[14] Monophasic synovial sarcoma and poorly differentiated synovial sarcoma creates a problem for pathologists when it comes to the differential diagnosis of synovial sarcoma. This is due to the monophasic type having uniform spindle cells.[15] This feature of monophasic synovial sarcomas causes it to be a challenge to differentiate monophasic synovial sarcoma from sarcomatoid squamous cell carcinoma, fibrosarcoma, malignant spindle cell melanoma, malignant peripheral sheath, leiomyosarcoma, Ewings Sarcoma/PNET, malignant solitary fibrous tumor, and atypical carcinoid tumor.[15] This challenge arises since the monophasic variant of synovial sarcoma cytologic features is usually bland, a uniform nucleus, and evenly distributed chromatin insignificant mitotic activity and the absence of necrosis.[15] This makes the use of molecular pathology and immunocytochemistry unremarkable in terms of detecting monophasic synovial sarcoma.[15] Due to the nature of monophasic synovial sarcoma only consisting of spindle cells and lack epithelial cells as with biphasic synovial cancer, an effective tool used to differentiate the two types is an EMA(epithelial membrane antigen). An EMA is an effective marker used to detect the epithelium nature of neoplastic cells.[16] A variety of soft tissue tumors lack immunoreactivity to EMA except for synovial sarcomas and epithelioid sarcoma.[16] However, EMA is not sufficient enough to differentiate between monophasic sarcoma and biphasic synovial sarcoma. The use of cytokeratin AE1/AE3 immunostain illustrates the biphasic synovial sarcoma.[15] When detecting the spindle cell nature of synovial sarcoma, typically positive readings are found with CD99 and BCL-2.[15] Currently, the combination use of EMA, CA AE1/AE3, CK7 immunostain; as well as the detection of illustrating characteristic translocation of (X;18), which causes the fusion of SS18-SSX1, SS18-SSX2 and on rare occasions SS18-SSX4. This combination of techniques provided the highest yield for detecting differentiation synovial sarcoma.[15]

Biphasic Synovial Sarcoma

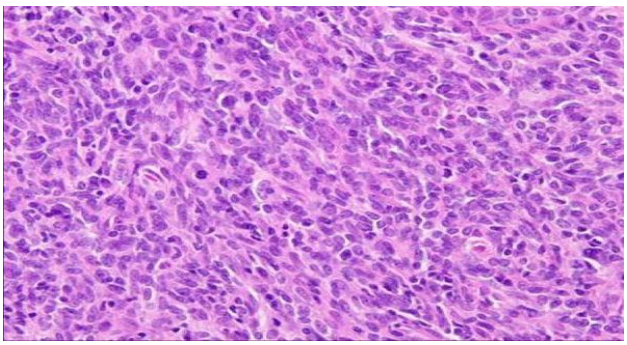
Biphasic Synovial Sarcoma contrives of Epithelial and Spindle cell elements, which ensue in varying proportions. Morphologically all of the subtypes can be identified by a specific t(X;18) (p11.2; q11.2) chromosomal translocation.[17] Biphasic Synovial Sarcoma has a very stereotypic histologic appearance therefore it is readily diagnosed. However, the monophasic variant is more difficult to recognize due to overlapping appearances with other spindle and round-cell sarcomas (Evans 1980, Meis-Kindblom et al. 1996, Folpe et al.[18] Adjunctive morphologic or cytogenetic techniques are needed to confirm the diagnosis of synovial sarcoma Usually, some patients come with the same symptoms, however, are later are excluded as another type of sarcomas such as metastatic carcinoma or benign epithelioid schwannoma.[17]

To identify a Biphasic sarcoma under a light microscope, the features should be supported as following

Any areas with a distinct biphasic pattern including epithelioid tumor cells forming glands, solid cords or strands as well as a spindle cell, fibrosarcoma-like component. Whereas the features for a monophasic synovial sarcoma can include the presence of highly uniform spindled cells with a higher nuclear to cytoplasmic ratio arranged in sweeping fascicles and whorls as well as alternating cellular and pericellular areas.[18]



Synovial sarcoma; biphasic glandular structures are formed amid a spindle cell background (x200).[2]



Higher magnification of Biphasic synovial sarcoma specimen

II. METHODS

The data presented here were gathered via Research Gate, National Center for Biotechnology Information, PubMed, and Google Scholar to identify peer-reviewed articles regarding the surgical implications of synovial sarcomas.

III. Review

Surgical implications

The treatment of STS is primarily surgical removal of the tumor. When it comes to surgical removal of tumors that can be done by one of the three types of margins in surgery; Intralesional, Marginal, and Wide. Intralesional margin implies that the surgery is a direct shot to the tumor that would result in scooping out the tumor without hurting the blood vessels, bone or nerves surrounding It, but it leaves behind microscopic crumbs of a tumor with the potential of the tumor growing back.[19] In which, it is not ideal in STS.

The wide margin method comes with cutting off normal tissue along with the tumor, therefore, resulting in the removal of blood vessels, bone, and nerves around the tumor and then postoperatively medicate the dysfunctional consequences.[19] The marginal margin method is considered ideal in STS. With this method, the tumor is being peeled off without hurting the blood vessels, bone, and nerves. Theoretically, the chance of small pieces of tumor left behind with the ability to grow back is very high therefore radiation therapy is done post-operative with results in the sterilization of the reactive zone that are small parts of tumors left behind. This will kill the edge of the tumor left behind and also preserve the function of the limb with a very minimal chance of the tumor growing back.[19]

Chemotherapy

To sum up the radiation therapy in STS cases, radiation therapy is usually given after surgery which is known as adjuvant treatment. As described in the introduction, radiation is usually done to kill leftover tumor cells. Radiation can affect the healing of wounds during surgery, so radiation chemotherapy starts after 25-30 days of surgery.[20] Surgery remains the chief treatment for primary synovial sarcoma regardless of adjuvant/neoadjuvant chemotherapy.[20] Neoadjuvant chemotherapy has not been very successful if considered as a standard solution to every synovial sarcoma patient. Neoadjuvant chemotherapy is considered successful in cases such as induction therapy. Phase II trial of neoadjuvant treatment, with the significance of toxicity, was witnessed when doxorubicin and ifosfamide were used to treat patients.[20] Either type of chemotherapy is recommended in high-risk patients only generally it is considered as the standard treatment for patients undergoing locally advanced or metastatic disease.[20] There are also chances of perioperative chemotherapy, but so far it is contentious. However further improvement to fight this disease is being researched.

Palliative chemotherapy

In the cases of STS, palliative chemotherapy is considered to be poor with very few cases that benefited from this procedure. Gemcitabine/docetaxel chemotherapy helps to a very little extent in STS patients and now it is not usually recommended.[21]

Novel treatment options under development

Pazopanib is the most popular in terms of targeted therapies for STS patients however there is a variety of other classes of targeted therapy that have been proven beneficial in helping STS patients such as epigenetic regulators and immunomodulators until now.[21] On the same hand, the majority has failed to provide long-lasting effects on STS.

Immunotherapy

The most promising approach in Synovial sarcoma clinical testing so far has been the use engineered T-Cells directed against the NY-ESO-! Cancer agents.[21] These patients were treated with lymphodepleting preparative chemotherapy followed by T cells transduced with NE-ESO-1 reactive T cell receptor resulting in tumor regression.[21]

Promising pre-clinical targeted therapies

As discussed above, a variety of preclinical studies have failed to show any sort of beneficiary for Soft tissue sarcoma patients. However, it has been suggested that the presence of SS18-SSX fusions have the potential to defenselessness fragility of STS tumor cells towards DDR inhibitors.[22] It can be done by the creation of a replication fork stress phenotype along with various DDR inhibitors.[22] These are currently being held in the testing phase for the malignancies with positive results in certain histology. This shows light of hope that with further clinical testing it might have the potential to be proven beneficial for STS patient's recovery.

I. Future direction

The combination of surgical resection and radiation therapy is the standard treatment for synovial sarcoma. The use of molecular agents and immunological agents is under investigation; however, showing great promise. Researchers are hopeful for more clinical trials for synovial sarcoma, in the upcoming years.

The only molecular agent approved for the treatment of synovial sarcoma is pazopanib, as it has been linked to a better outcome with the risk of pneumothorax, which is a consequence of synovial sarcoma in lung lesions. There have been trials undergone with other molecular drugs; some being: WNT–β-catenin, the protein kinase B, and more recently, anaplastic lymphoma kinase. However, no new molecular agent has shown significant improvement, this past decade.

Therapy by immunological agents first showed promise in 1982, when lymphokine-activated killer cells (LAK), displayed the ability to destroy several of tumor cells, SS included. This research is thought to be what inspired curiosity within immunology treatment; as, there are currently two methods undergoing clinical treatment. The first treatment involves T cells, and they are arranged to detect the cancerous, NY-ESO-1 peptide. The second approach utilizes a dendritic cell attacking agent that expresses NY-ESO-1. The results of both

studies are highly awaited; as, there is a lack of growth in immunologic agents against cancer.

To summarize, the current treatment course for synovial sarcoma is the combination of radiation and surgery. Molecular agents, ifosfamide, and pazopanib are the chosen treatments for patients with advanced synovial sarcoma. Research in synovial sarcoma treatment approaches has been quite limiting; as it is an extremely aggressive cancer. However, due to this tumor's diverse nature, it will require advanced levels of research to match it.[4]

REFERENCES

1. Baird, K., Davis, S., Antonescu, C. R., Harper, U. L., Walker, R. L., Chen, Y., … Meltzer, P. S. Gene Expression Profiling of Human Sarcomas: Insights into Sarcoma Biology. *Cancer Research*, 2005; *65*(20): 9226–9235. doi: 10.1158/0008-5472.can-05-1699.
2. Randall R, Ward R, Hoang BH. Chapter 5. Musculoskeletal Oncology. In: Skinner HB, McMahon PJ. eds. *Current Diagnosis & Treatment in Orthopedics, 5e* New York, NY: McGraw-Hill; http://accessmedicine.mhmedical.com/content.aspx?bookid=675&sectionid=45451711. Accessed March, 2020; 09.
3. Fritchie KJ, John I. Soft Tissue and Bone Pathology. In: Reisner HM. eds. *Pathology: A Modern Case Study, 2e* New York, NY: McGraw-Hill;. http://accessmedicine.mhmedical.com/content.aspx?bookid=2748&sectionid=230844672. Accessed March, 2020 09.
4. Mentzel T, Brenn T. Lipogenic Neoplasms. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. *Fitzpatrick's Dermatology, 9e* New York, NY: McGraw-Hill;. http://accessmedicine.mhmedical.com/content.aspx?bookid=2570&sectionid=210436887. Accessed March, 2020; 09.
5. Guadagnolo, B. Ashleigh, et al. "Long-Term Outcomes for Synovial Sarcoma Treated With Conservation Surgery and Radiotherapy." *International Journal of Radiation Oncology*Biology*Physics*, 2007; 69(4): 1173–1180., doi:10.1016/j.ijrobp.04.056.
6. Bergh, P., Meis-Kindblom, J. M., Gherlinzoni, F., Berlin, R., Bacchini, P., Bertoni, F., Kindblom, L.-G. Synovial sarcoma. *American Cancer Society*, 1999; *85*(12): 2596–2607. doi:10.1002/(sici)1097-0142(19990615)85:12<2596::aid-cncr16>3.0.co;2-kdoi:10.1002/(sici)1097-0142(19990615)85:12<2596::aid-cncr16>3.0.co;2-k
7. Foo, W. C., Cruise, M. W., Wick, M. R., & Hornick, J. L. Immunohistochemical Staining for TLE1 Distinguishes Synovial Sarcoma From Histologic Mimics. *American Journal of Clinical Pathology*, 2011; *135*(6): 839–844. doi: 10.1309/ajcp45ssnaopxyxu.
8. Hartel, P. H. Unusual histology in primary pulmonary synovial sarcoma: Pearls to avoid misdiagnosis. *Medical Case Reports and Reviews*, 2018; *2*(1). doi: 10.15761/mcrr.1000105.
9. Nielsen, T. O., Hsu, F. D., Oconnell, J. X., Gilks, C. B., Sorensen, P. H., Linn, S., … Rijn, M. V. D. Tissue Microarray Validation of Epidermal Growth Factor Receptor and SALL2 in Synovial Sarcoma with Comparison to Tumors of Similar Histology. *The American Journal of Pathology*, 2003; *163*(4): 1449–1456. doi: 10.1016/s0002-9440(10)63502-x.
10. Miettinen, M., Lehto, V.-P., & Virtanen, I. Keratin in the epithelial-like cells of classical biphasic synovial sarcoma. *Virchows Archiv B Cell Pathology Including Molecular Pathology*, 1982; *40*(1): 157–161. doi: 10.1007/bf02932860.
11. He, X., Xiong, B., Zhon, T., Lan, T., Chen, M., Peng, R. Zhang, H. Diagnostic value of TLE1 for synovial sarcoma: immunohistochemical analyses of genetically confirmed synovial sarcomas and nonsynovial sarcomas. *International Journal of Clinical and Experimental Pathology*, 2016; *9*(4): 4339–4350.
12. Stacchiotti, Silvia, & Tine, B. A. V. (n.d.). Synovial Sarcoma: Current Concepts and Future Perspectives. Retrieved from https://ascopubs.org/doi/full/10.1200/JCO, 2017: 75-1941.
13. Jayasooriya, P. R., Madawalagamage, L. N., Mendis, B. R. R. N., & Lombardi, T. Diagnostic Approach to Synovial Sarcoma of the Head and Neck Illustrated by Two Cases Arising in the Face and Oral Cavity, 2016; 22. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4868929/
14. Rong, R., Doxtader, E. E., Tull, J., Roza, G. de la, & Zhang, S. Metastatic poorly differentiated monophasic synovial sarcoma to lung with unknown primary; a molecular genetic analysis, 2009; 25. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2810002/
15. https://www.omicsonline.org/open-access/metastatic-monophasic-synovial-sarcoma-a-challenging-diagnosis-on-fine-needle-aspiration-with-broad-differential-diagnosis-DPO-1000114.php?aid=73877
16. https://www.ncbi.nlm.nih.gov/pubmed/2993153
17. https://www.orpha.net/data/patho/GB/uk-synovialsarcoma.pdf
18. https://www.tandfonline.com/doi/pdf/10.3109/17453679908997840
19. Desar, Ingrid M E, et al. "Systemic Treatment for Adults with Synovial Sarcoma." *Current Treatment Options in Oncology*, Springer US, 2018; 7. www.ncbi.nlm.nih.gov/pmc/articles/PMC5842271/
20. Yang, M., Zhong, N., Zhao, C. *et al.* Surgical management and outcome of synovial sarcoma in

the spine. *World J Surg Onc*, 2018; 16: 175. https://doi.org/10.1186/s12957-018-1471-x.

21. Cassier PA, Lefranc A, Amela EY, Chevreau C, Bui BN, Lecesne A, et al. A phase II trial of panobinostat in patients with advanced pretreated soft tissue sarcoma. A study from the French Sarcoma Group. Br J Cancer, 2013; 109(4): 909–914. doi: 10.1038/bjc. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Gronchi A, Maki RG, Jones RL. Treatment of soft tissue sarcoma: a focus on earlier stages. Future Oncol (Lond), 2017; 13(1): 13–21. doi: 10.2217/fon-2016-0499. [PubMed] [CrossRef] [Google Scholar]