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A RETROSPECTIVE COHORT STUDY OF SOFT TISSUE AND BONE SARCOMAS AT A TERTIARY CARE CENTRE

General Surgery

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ABSTRACT

Background: Sarcoma, though a rare cancer group, is associated with considerable mortality and morbidity in the overall population and the data is insufficient in Saudi Arabia. The objective of this descriptive study is to characterize the disease and to correlate certain clinical response to the practiced management in addition to better understanding of sarcoma.

Methods: This retrospective study was conducted at King Fahad Medical City, Riyadh(KFMC) over a period from 2009 to 2013. The bones and soft tissue sarcoma cases were categorized as newly diagnosed and relapsed cases.

Results: Among the total 43 patients 41 were newly diagnosed and 2 were relapsed cases of which 26 (60.5%) belonged to soft tissue sarcoma(STS)and 17(39.5%) had bone sarcoma(BS).Average age was 33.6 years (Mean ± S.D:33.51 ± 17.66). Twenty-nine patients had localized disease whereas 14 patients were already having metastatic disease at presentation. The median follows up time of disease free survival was 39 months. Kaplan – Meier survival curve showed significant association between disease free survival (90.9%) and survival with recurrence (87.5%), P-value 0.036. Tumor grade (P = 0.045) and combined therapy (surgery+/-chemotherapy+/- radiotherapy)(P = 0.047) were statistically significant determinant for survival.

Conclusion: The median disease free survival was comparable for our study patients to the reported literature. Surgery combined with chemotherapy with or without radiotherapy either in neo-adjuvant or adjuvant setting carries significantly better overall survival as compared to surgery alone. Future prospective multi-center study is needed in order to characterize and understand sarcoma in our population.

KEYWORDS

Soft tissue sarcoma, Bone sarcoma, Tumor histology, Disease manifestation, Metastasis, Surgical resection, Chemotherapy effect, Recurrence, outcome.

BACKGROUND:

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise approximately 1 % of all adult malignancies and 12 % of pediatric cancers**[**1,2**].**The majority of diagnosed sarcomas are soft tissue sarcomas, while malignant bone tumors make up just over 10% of sarcomas. It is a variety of malignant tumor that arises from skeletal and extra skeletal connective tissues, including the peripheral nervous system. The majority of soft tissue sarcomas (STS) present in the extremities; however, many other sites can be affected, including the retro peritoneum, chest wall, head and neck, and subcutaneous tissues. The diversity and rarity of occurrence make their comprehensive understanding a difficult task.

Broadly, sarcomas are divided into two distinct categories i.e. Bone sarcoma and Soft tissue sarcoma. Approximately 80 percent of sarcomas originate from soft tissue and the rest from bone. In nearly all instances, sarcomas are thought to arise de novo and not from a pre-existing benign lesion. Most cases have no clearly defined etiology, but a number of associated or predisposing factors have been identified including genetic predisposition (eg, Li-Fraumeni syndrome, neurofibromatosis type I), exposure to radiation therapy or chemotherapy, chemical carcinogens,virus, chronic irritation, and lymphedema **[3].** Complete staging and treatment planning by multidisciplinary team of cancer specialists is required to determine the optimal treatment for these patients **[4].**However, the histological grade of the tumor remains one of the most important prognostic variables for soft tissue sarcoma**[5,6,7**]. The most common pattern of spread is hematogenous, predominantly to the lung. Spread to regional nodes is infrequent except for certain histology **[8,9].** Surgical resection remains the mainstay of a potential cure for localized, potentially resectable retroperitoneal sarcoma and longer disease-free survival for few selected patients with metastatic disease[10].The role of chemotherapy is still uncertain for soft tissue sarcoma whereas some bone sarcomas are chemo-sensitive and therefore, chemotherapy is considered as an integral part of their treatment protocol**[4].**

With this background we want to perform a retrospective study to report our experience in treating sarcoma patients at KFMC specially the tumor biology, histological types, disease manifestation and outcome of different modalities of treatment in our patient population.

METHODS:

A retrospective study of bones and soft tissue sarcoma cases seen at King Fahad Medical City over a period of five years starting from 2009 till 2013.Data was collected retrospectively by reviewing the patient's file from the medical record. Adult patients with soft tissue and bone sarcomas, age 12 years and above. All the non-gastrointestinal stromal tumor(GIST)sarcoma cases operated/treated under two different specialists in the field were included. Patients age below 12 years,GIST and other Sarcoma cases managed by other surgeons,all cases of leiomyosarcoma of uterus managed by gynae-oncology surgeons were excluded from the study.

Statistical Analysis Procedure:

Baseline and demographic characteristics were presented in frequencies and percentages. Whereas all continuous variables were expressed as Mean ± S.D. The evaluation of primary ends points and outcome with complete follow-up assessment of the study was evaluated by difference response rate of treated patients by combined and single therapy. Kaplan – Meier survival curves were used to estimate the disease-free survival (DFS) rate and survival with a recurrence rate of the patients. Pearson's Chi-square / Fisher's exact test was applied according to whether the cell expected frequency is smaller than 5. P – value< 0.05 was considered as statistically significant. All data was entered and analyzed through statistical package SPSS version 22.

RESULTS:

Out of total 43 patients, 41(95.3%) newly diagnosed and 2(4.7%) relapsed cases were seen at KFMC during the study period. The average age of the patient was 33.6 years (Mean ± S.D:33.51 ± 17.66)of which 23 (53.5%) patients were male and 20(46.5%) were female. A number of the patients, 38(88.4%) had no co-morbidities with only five (11.6%) had more than one co-morbidities. The majority of the cases seen were soft tissue sarcomas 26 (60.5%) and the rest 17(39.5%) were bone sarcomas. A wide variety of histological

subtypes were encountered of which (i) Ewing's sarcoma 9(20%) counts the most followed by (ii) osteosarcoma 7(16.3%) (iii)rhabdomyosarcoma 5(11.6%) (iv) liposarcoma 4(9.3%) (v) dermatofibrosacroma 4(9.3%) (vi) synovial sarcoma 4(9.3%) (vii) Nerve sheath tumor 3(7%) (viii) spindle cell neoplasm 2(4.7%) (ix) giant cell tumor 2 (4.7%) (x)chondrosarcoma 1(2.3%)and (xi) Epithelioid sarcoma 1(2.3%) respectively. Fourteen (32.6%) of the cases were having distant metastasis at presentation.

Average tumor size was 9cm (Mean ± S.D:9.4 ± 4.9) with 20 (46.5%)high histological grade, and 23 (53.5%) low grade respectively. Microscopic negative resection margin was achieved in 30 (69.8%) patients and 10 (23.3%) patients had a positive margin. Negative macroscopic free margin was possible in 33(76%) patients and only 7(16%) patients had a positive resection margins grossly.

Thirty-one (72.1%) patients received combined treatment (surgical resection plus Radiotherapy or chemotherapy or both chemo-radiation therapy) either adjuvant or neo-adjuvant setting. However, twelve (27.9%)) patients had undergone curative resection alone without any additional therapy. No surgical treatment was offered for three (6.9%) patients as the tumor was unresectable and already advanced stage of presentation. The postoperative complications were noted in only two (4.6%) cases with one had wound infection and the other suffered from deep vein thrombosis (DVT). The median follow-up period was 26(3-96) months. Four patients lost to follow up with us.

There was statistically significant (P = 0.045) association noted between histological grade and survival status (alive or dead). In other word, seventeen (60.7%) patients were alive and one (12.5%) patient was dead belonging to low histological grade. On the other hand, eleven (39.3%) patients were alive and seven (87.5%) patients were dead that belonged to high histological grade.

In the same way, there was also statistically significant (P = 0.047) association found between combination therapy and surgery alone in regards to survival status. i.e. eighteen (64.3%) patients survived who received treatment with combined therapy. Whereas ten (35.7%) patients were alive who were treated with surgery alone.

Table -1: Clinical Characteristics of the Patients (n = 43)

Variables	Categories	n (n%)
Comorbidities	Yes	5 (11.6%)
	No	38 (88.4%)
Histological Types	Chondrosarcoma	1 (2.3%)
	Dermatofibroscarcoma	4 (9.3%)
	Epitheloid sarcoma	1 (2.3%)
	Ewing's Sarcoma	9 (20.9%)
	Giant Cell tumor	2 (4.7%)
	Liposarcoma	4 (9.3%)
	Malignant Phylloid	1 (2.3%)
	Nerve Sheath tumor	3 (7.0%)
	Osteosarcoma	7 (16.3%)
	Rhabdomnyoscarcoma	5 (11.6%)
	Spindle cell Neoplasm	2 (4.7%)
	Synovial sarcoma	4 (9.3%)
Histologic Grade	Low Grade	23 (53.5%)
	High Grade	20 (46.5%)
Resection Margin (Microscopic)	Negative	30 (69.8%)
	Positive	10 (23.3%)
	Not Applicable	3 (7.0%)
Diagnosis	Newly Diagnosed	41 (95.3%)
	Relapse	2 (4.7%)
Treatment Modality	Combine Therapy	31 (72.1%)
	Single Therapy (Surgery)	12 (27.9%)
Resection Margin (Macroscopic)	Negative	33 (76.7%)
	Positive	7 (16.3%)
	Not Applicable	3 (7.0%)
Recurrence	Recurrence	8 (25.8%)
	Without recurrence	23 (74.2%)
Metastasis on presentation	Yes	14 (32.6%)
	No	29 (67.4%)
Status	Alive	28 (77.8%)
	Dead	8 (22.2%)

Table – 2: Impact and Association between outcome and Clinical Parameters

		Status		P - value
		Alive (n = 28)	Dead (n = 8)	
Histological Grade	Low Grade	17 (60.7%)	1 (12.5%)	*0.041
	High Grade	11 (39.3%)	7 (87.5%)	
Resection Margin (Microscopic)	Negative	20 (74.1%)	4 (57.1%)	0.394
	Positive	7 (25.9%)	3 (42.9%)	
Diagnosis	Newly Diagnosed	26 (92.9%)	8 (100.0%)	0.437
	Relapse	2 (7.1%)	0 (0.0%)	
Treatment modality	Combine Therapy	18 (64.3%)	8 (100.0%)	* 0.047
	Single Therapy (Surgery)	10 (35.7%)	0 (0.0%)	
Resection Margin (Macroscopic)	Negative	23 (85.2%)	4 (57.1%)	0.135
	Positive	4 (14.8%)	3 (42.9%)	
Recurrence	Recurrence	5 (20.8%)	3 (50.0%)	0.148
	No Recurrence	19 (79.2%)	3 (50.0%)	

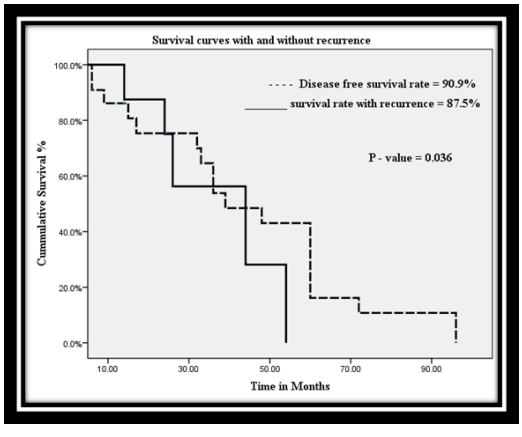
Table –3: Relationship between disease status(Recurrence or no recurrence) with clinical parameters

		Recurrence	Without Recurrence	P - value
Histological Grade	Low Grade	3 (37.5%)	15 (65.2%)	0.302
	High Grade	5 (62.5%)	8 (34.8%)	
Resection Margin (Microscopic)	Negative	4 (57.1%)	20 (87.0%)	0.120
	Positive	3 (42.9%)	3 (13.0%)	
Diagnosis	Newly Diagnosed	7 (87.5%)	22 (95.7%)	0.419
	Relapse	1 (12.5%)	1 (4.3%)	
Treatment modality	Combine Therapy	7 (87.5%)	14 (60.9%)	0.165
	Single Therapy (Surgery)	1 (12.5%)	9 (39.1%)	
Resection Margin (Macroscopic)	Negative	5 (71.4%)	22 (95.7%)	0.128
	Positive	2 (28.6%)	1 (4.3%)	

Among those with low histological grade, three (37.5%) patients had recurrence and fifteen (65.2%) patients had no recurrence. Similarly, five (62.5%) patients had recurrence and eight (34.8%) had no recurrence that related to high histological grade. Overall, relationship between recurrence and no recurrence of sarcoma with other clinical parameters also showed no statistically significant differences (P: 0.120- 0.419).

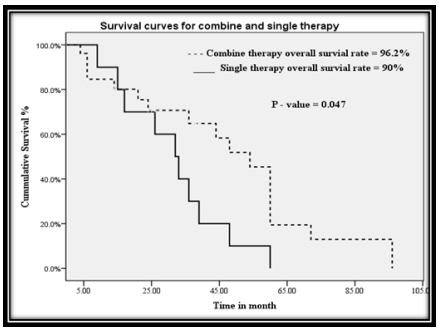
The median follow-up time of survival with recurrence was 44 months. Whereas the follow up time of disease free survival was 39 months. Survival curve shows significant association between disease free survival (90.9%) and survival with recurrence (87.5%), P-value 0.036. [Figure – 1]

Figure – 1: Survival curves with and without recurrence:



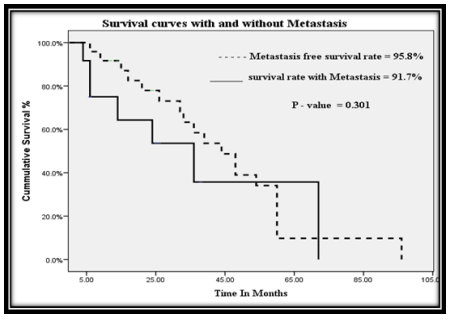
The median follow-up time of survival with combine therapy was 54 months and the median follow up time of survival with single therapy was 32 months. Combined therapy overall survival rate (96.2%) was significantly higher compared to single therapy (surgery alone) overall survival rate (90%); P- value 0.047.[Figure – 2]

Figure – 2: Survival curves for combine and single therapy:



The median follow-up time of survival with Metastasis was 36 months and the median follow up time of survival without Metastasis was 44 months. Survival curve with or without metastasis on presentation revealed metastasis free survival rate of (95.8%) compared to survival rate with metastasis (91.7%) with P-value 0.301. [Figure – 3]

Figure – 3: Survival curves with and without Metastasis:



DISCUSSION:

King Fahad Medical City (KFMC) Hospital is one of the largest tertiary care oncology referral centers in the Saudi Arabia (SA). This study represents the epidemiology, tumor characteristics, response to treatment, outcome of sarcoma (soft tissue and bone) and five-year survival of the patients treated at surgical oncology and orthopedic department at KFMC over a period of five years.

Current study is first of its kind in SA to highlight the pattern of the disease and its outcome as oppose to previous studies from Saudi Arabia which mainly focus on bone sarcomas or individual tumor type only. Relatively small number of the patients in this study is consistent with the overall low incidence and rarity of the disease **[10, 11, 12].**Age is an important determinant of sarcoma occurrence. Based on current statistics provided by the NCHS and SEER, from 2004–2008, the mean age at diagnosis for STS and BS is 58 and 40 years of age, respectively**. [13]** This finding is discordant with what results we get in current study, the mean age was33.51 and 17.66 years for STS and BS, respectively. This is clearly indicating that a younger age group is being affected by the disease in this part of the world, that may have a genetic, lifestyle or environmental etiology as described by the Merletti F et.al in his Europe based-study, consisting of 96 cases and 2,632 controls. He found a significant increase in soft tissue sarcoma risk among gardeners and tobacco smokers (adjusted OR 4.1, 95% CI 1.00, 14.00). **[14]** No clear gender preponderance was recognized in this study which is in line with most of the studies from US and Europe. **[15, 16]**

When the talk is about the overall prognosis and outcome of the sarcomas; the age older than 60 years, positive resection margin, tumor size ≥ 5cm, high histological grade, deep location, no adjuvant therapy all are considered as unfavorable characteristics for local tumor recurrence, metastatic risk, disease free survival and overall survival which is clearly mentioned in many previous studies **[17, 18, 19].**Results of this study are in accordance with the findings of the available evidence with majority (70 %) of patients had a negative resection margins and about 54 % were low histological grade that is associated with slightly improved survival in this study participants. This fact is supported by achieving a statistically significant (P = 0.045) association between histological grade and survival status with presence of low grade tumor histology is associated with improved survival.

Neo-adjuvant chemotherapy or chemo-radiation has been evaluated in single and multicenter studies in patients with high-grade tumor. Kraybill WG1 et al in his phase 2 multicenter study of neo-adjuvant chemotherapy and radiotherapy in the management of soft tissue sarcomas and Mullen JT1in his retrospective study has concluded that preoperative chemo radiation followed by resection and post-operative chemotherapy with a doxorubicin based regimen improves local control of the disease, DFS and OS rates in patients with high grade STS of extremity and body wall; although, pre-operative chemo radiation was associated with significant short-term toxicities **[20, 21].**Similar results were observed in the current study with median follow up time of survival with combine therapy is 54 months and the median follow up time of survival with single therapy is 32 months. Combined therapy overall survival rate (96.2%) was significantly higher compared to single therapy (surgery alone) overall survival rate (90%); P- value 0.047.

Available evidence from meta-analysis and randomized clinical trials suggests that post-operative chemotherapy improves relapse-free survival (RFS) in patients with STS of extremities. Nevertheless, data regarding OS advantage are conflicting **[22, 23, 24, 25].** Our study revealed significantly higher combined therapy overall survival rate compared to surgery alone contradicting current evidence. The improved DFS and OS in current study could be contributed by younger study population, absence of co-morbidities, achieving negative margins in majority of cases and no metastasis in many of them. Low rate of perioperative and chemo-radiotherapy related complication is a reflection of the similar factors that could have contributed to improved survival.

The median follow up time of survival with Metastasis is 36 months without Metastasis is 44 months. Survival curve with or without metastasis on presentation revealed metastasis free survival rate of (95.8%) compared to survival rate with metastasis (91.7%) with P-value 0.301. Patient who have metastatic disease on presentation carries poor prognosis with no disease free interval **[26, 27].** Since there are no data to support the optimal management of patients presenting with metastatic disease, the current guidelines are intentionally nonspecific about the treatment options for this group of patients. More recently, a number of targeted therapies have shown promising results in patients with certain histological types of advanced or metastatic STS.

All patients with Bone and STS should be evaluated and managed by a dedicated multidisciplinary team who have extensive expertise and experience in the treatment of sarcoma. Limitation of this study was the small number of patients with variety of treatment strategies. Therefore, the analysis was based on small heterogeneous group of population. In addition to that a small number of patients lost to follow up.

CONCLUSION:

Management of Sarcoma is challenging and associated with considerable mortality and morbidity in Saudi population**.** Study population at KFMC exhibits a very diverse behavior in terms of tumor biology, disease manifestation, their course and outcome. Treatment options should be decided by a multidisciplinary team with extensive experience in the treatment of sarcoma and is dependent on the patient's age, performance status, comorbidities, disease stage, location and histological subtype. Older age group, large tumor size, high grade tumors, positive resection margin carries poor prognosis in regards to DFS and OAS. Combined therapy with surgery and chemo radiation shows clear benefit in terms of overall survival as compared to surgery alone. Therefore, adjuvant chemotherapy may be beneficial in selected patients with sarcoma. Further multicenter prospective studies will help understanding the sarcoma better in this region. Raising public awareness and periodic active surveillance is also essential.

Abbreviations:

Not applicable

Declarations

1. Ethics approval and consent to participate We conducted this study after approval of Institutional Review Board(IRB), IRB log No:13-145, KACST, KSA: H-01-R-012; IRB registration number with OHRP/NIH, USA: IRB-00008644, Federal Wide Assurance approval, NIH/ USA: FWA-00018774.No potential conflict of interest relevant to this article was noted.
2. **Consent to publish**

Not applicable

3. Availability of data and materials
   The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.
4. **Competing interests**
   There is no competing interest in regards to this study.
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REFERENCES

1. Miller RW, Young JL Jr, Novakovic B. Childhood cancer. Cancer 1995; 75:395.
2. Fletcher CDM, Unni KK, Mertens F. World Health Organization Classification of tumours: Pathology and Genetics of tumours of soft tissue and bone, IARC Press, Lyon 2002.
3. Brennan M, Singer S, Maki R, O'Sullivan B. In: Cancer: Principles and Practice of Oncology. DeVita VT, Hellman S, Rosenberg SA, editor. Vol. 8. 2008. Sarcomas of the soft tissues and bone; pp. 1742–1833.
4. Adult soft tissue sarcoma treatment. http:// cancer. gov/ cancertopics/pdq /treatment/adult-soft-tissue-sarcoma/ health professional #Section_229.
5. Mazanet R, Antman Karen H. Sarcoma of Soft Tissue and Bone. Cancer.1991;68:463–473. doi: 10.1002/1097-0142(19910801)68:3<463:AID-CNCR2820680304>3.0.CO;2-E.
6. Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchere D, Sastre X, Vilain MO, Bonichon F, N'guyen BB. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: A study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 91. 2001;10:1914–26.
7. Vraa S, Keller J, Nielsen OS, Sneppen O, Jurik AG, Jensen OM. Prognostic factors in soft tissue sarcomas: the Aarhus experience. Eur J Cancer 34.1998;12:1876–82.
8. Christie-Large M, James SL, Tiessen L, et al. Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas. Eur J Cancer 2008; 44:1841.
9. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993; 217:72.
10. American Cancer Society: Cancer Facts and Figures 2017. Atlanta, Ga: American Cancer Society, 2017. Available online. Last accessed July 20, 2017.
11. Wibmer C, Leithner A, Zielonke N, et al.: Increasing incidence rates of soft tissue sarcomas? A population-based epidemiologic study and literature review. Ann Oncol 21 (5): 1106-11, 2010.
12. Surveillance, Epidemiology, and End Results (SEER) Program (http://www.seer.cancer.gov). Last accessed July 20, 2017
13. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK: SEER Cancer Statistics Review, 1975–2008. http://seer.cancer.gov/csr/1975_2008/ based on November 2010 SEER data submission, posted to the SEER web site, 2011, National Cancer Institute. Bethesda, MD
14. Merletti F, Richiardi L, Bertoni F, Ahrens W, Buemi A, Costa-Santos C, Eriksson M, Guénel P, Kaerlev L, Jöckel KH, Llopis-Gonzalez A, Merler E, Miranda A, Morales-Suárez-Varela MM, Olsson H, Fletcher T, Olsen J: Occupational factors and risk of adult bone sarcomas: a multicentric case–control study in Europe. Int J Cancer. 2006, 118 (3): 721-727. 10.1002/ijc.21388
15. Lahat G, Lazar A, Lev D: Sarcoma epidemiology and etiology: potential environmental and genetic factors. SurgClin North Am. 2008, 88 (3): 451-481. 10.1016/j.suc.2008.03.006
16. Cancer Incidence in Five Continents, Volume IX. IARC Scientific Publications No. 160. Edited by: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P. 2007, IARC, Lyon,
17. Kasper B, Ouali M, van Glabbeke M, et al.: Prognostic factors in adolescents and young adults (AYA) with high risk soft tissue sarcoma (STS) treated by adjuvant chemotherapy: a study based on pooled European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62771 and 62931. Eur J Cancer 49 (2): 449-56, 2013.
18. Trovik LH, Ovrebo K, Almquist M, et al.: Adjuvant radiotherapy in retroperitoneal sarcomas. A Scandinavian Sarcoma Group study of 97 patients. ActaOncol 53 (9): 1165-72, 2014.
19. Coindre JM1, Terrier P, Bui NB, Bonichon F, Collin F, Le Doussal V, Mandard AM, Vilain MO, Jacquemier J, Duplay H, Sastre X, Barlier C, Henry-Amar M, Macé-Lesech J, ContessoG.Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J ClinOncol. 1996 Mar;14(3):869-77.
20. Kraybill WG1, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH, Lucas DR, Harmon DC, Letson GD, Eisenberg B. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. Cancer. 2010 Oct 1;116(19):4613-21. doi: 10.1002/cncr.25350.
21. Mullen JT1, Kobayashi W, Wang JJ, Harmon DC, Choy E, Hornicek FJ, Rosenberg AE, Chen YL, Spiro IJ, DeLaney TF. Long-term follow-up of patients treated with neoadjuvant chemotherapy and radiotherapy for large, extremity soft tissue sarcomas. Cancer. 2012 Aug 1;118(15):3758-65. doi: 10.1002/cncr.26696. Epub 2011 Dec 16.
22. Pervaiz N1, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M.A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008 Aug 1;113(3):573-81. doi: 10.1002/cncr.23592.
23. Italiano A1, Delva F, Mathoulin-Pelissier S, Le Cesne A, Bonvalot S, Terrier P, Trassard M, Michels JJ, Blay JY, Coindre JM, Bui B.Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. Ann Oncol. 2010 Dec;21(12):2436-41. doi: 10.1093/annonc/mdq238. Epub 2010 May 3.
24. Fakhrai N1, Ebm C, Kostler WJ, Jantsch M, Abdolvahab F, Dominkus M, Pokrajac B, Kauer-Dorner D, Zielinski CC, Brodowicz T; Austrian Cooperative Soft Tissue Sarcoma Study Group.Intensifiedadjuvant IFADIC chemotherapy in combination with radiotherapy versus radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial. Wien KlinWochenschr. 2010 Nov;122(21-22):614-9. doi: 10.1007/s00508-010-1472-4. Epub 2010 Oct 22.
25. Le Cesne A1, Ouali M2, Leahy MG3, Santoro A4, Hoekstra HJ5, Hohenberger P6, Van Coevorden F7, Rutkowski P8, Van Hoesel R9, Verweij J10, Bonvalot S11, Steward WP3, Gronchi A4, Hogendoorn PC12, Litiere S2, Marreaud S2, Blay JY13, Van Der Graaf WT9.Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol. 2014 Dec;25(12):2425-32. doi: 10.1093/annonc/mdu460. Epub 2014 Oct 6.
26. Kane JM1, Finley JW, Driscoll D, Kraybill WG, Gibbs JF.The treatment and outcome of patients with soft tissue sarcomas and synchronous metastases. Sarcoma. 2002;6(2):69-73. doi: 10.1080/1357714021000022168.
27. Ferguson PC1, Deheshi BM, Chung P, Catton CN, O'Sullivan B, Gupta A, Griffin AM, WunderJS.Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. Cancer. 2011 Jan 15;117(2):372-9. doi: 10.1002/cncr.25418. Epub 2010 Sep 9.