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SOFT TISSUE SARCOMA; MANAGEMENT AND TREATMENT OUTCOME IN A TERTIARY HEALTH INSTITUTION IN NORTHERN NIGERIA

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Abstract

Soft tissue sarcoma constitutes 7% of all cancers in Nigeria. A complete staging of this tumour is important to evaluate the prognosis and plan the treatment in a multidisciplinary team. Management of sarcoma includes surgery, which involve partial or complete excision of the tumour mass. Surgery is the primary treatment modality for soft tissue sarcoma. Radiotherapy is useful in both localized and metastatic disease. Reports have shown the benefit of radiation therapy in decreasing recurrence rate in positive margin post excision. It is also useful for palliation of some symptoms. Chemotherapy has been shown to improve the survival of patients. Doxorubicin and Ifosfamide have shown better response in patients with these malignancies. The outcome of patients with soft tissue sarcoma depends on the margins' status post excision, performance status, grade, and stage of the disease.

MATERIALS AND METHODS

It is a five year retrospective study of patients with soft tissue sarcoma seen in the department of radiotherapy and Oncology, Usmanu Danfodiyo University teaching hospital. The treatment and overall survival at one year post diagnosis were reviewed with associating compounding variable.

RESULTS

A total of 123 patients were reviewed, out of which 69.9% of the patients had radiotherapy, and 64% of the patients who had radiotherapy received palliative dose. The commonest chemotherapy used was vincristine, which was used in 82% of the patients who had chemotherapy, while 76% received doxorubicin and 10% had ifosfamide.

The overall survival at one year was assessed in 112 patients. There was no significant difference between their age, gender, histological type and their survival at one year, however there was an association between the performance status (ECOG) and surgical excision status.

CONCLUSION

The outcome of patients with soft tissue sarcoma after diagnosis is determined by the performance status and the surgical excision margin. This will ultimately guide treatment of these groups of malignancies.

Keywords:

1. Introduction

Sarcomas are rare malignancies that arise from the mesenchymal tissues of the body and can affect the different regions, causing symptoms due to local tumour burden and distant spread where present.(1) They classically present as a growing painless mass. Several-months delays in presentation to a physician, establishment of a sarcoma diagnosis, and referral to a sarcoma center for treatment are not uncommon.(1)

In black Africans, there is paucity of information on soft tissue sarcoma (STS). The National Cancer Registry in Nigeria shows that this tumor constitutes about 7% of all cancer in Nigeria.(2)

For complete staging, a thorough physical ex-

amination, imaging, laboratory studies, and careful review of all biopsy specimens (including those from the primary tumor, lymph nodes, or other suspicious lesions) are essential.(1)(3)

Initial laboratory tests should include a complete blood count, basic blood chemistry, liver and renal function tests. Renal function tests are relevant for retroperitoneal lesions that may be in the region of the kidneys or ureters.(4) (5)

Plain radiographs are helpful in the evaluation of soft tissue tumours by demonstrating soft tissue remodeling, bone invasion, and soft-tissue calcification or ossification. However, imaging studies are not reliable in assessing the biological behaviour of soft tissue tumours. (5) (6)

Ccomputed tomography (CT) scans of the chest, abdomen, and pelvis are required to appropriately evaluate and stage STS. CT scan and MRI scans are necessary to adequately evaluate the primary lesion. CT scan will typically provide better bone detail while MRI is the definitive imaging modality for STS. MRI provides excellent contrast resolution within soft tissues, allows discernment of peritumoral edema, and acquires images in multiple viewing planes. (7) (8) (9) CT scan of the chest should always be performed when available to assess for pulmonary metastasis. Renal perfusion scans should be ordered for retroperitoneal lesions that would require irradiation. Imaging of the response to treatment with CT and MRI has been generally disappointing up to the present. Decrease in tumour size may occur, but does not correlate well with successful radiation or chemotherapy (10)

Biopsy of the primary tumor is essential for most patients presenting with soft-tissue masses. In general, any soft-tissue mass in an adult that is asymptomatic or enlarging, larger than 5 cm, or persists beyond 4 to 6 weeks should be biopsied.(6) The preferred biopsy approach is generally the least invasive technique required to allow a definitive histologic diagnosis and assessment of grade. In most centers, core-needle biopsy provides satisfactory tissue for diagnosis. (11) (12)

In the case of a suspected STS, biopsy should be performed prior to excision in order to avoid inadequate surgery. Two types of biopsies are commonly used: needle (fine needle aspiration and core needle biopsy) and open biopsy (incisional and excisional). Needle biopsies are less time consuming, relatively inexpensive, associated with minimal morbidity, limited soft-tissue contamination, and can be performed on an outpatient clinic setting. (13)

Histological diagnosis should be made according to the WHO Classification to determine the grade and stage of the tumour.(14) The grade should be provided in all cases where possible based on a recognized system.

Historically, four categories of surgical margin have been described histologically: intralesional, marginal, wide and radical as summarized below.

Intralesional: Margin runs through tumour and therefore tumour remains.

Marginal: Surgical plane runs through pseudocapsule (reactive zone). The local recurrence rate is high because of tumour satellites in the reactive tissue. There are however prognostic differences between a planned and unplanned marginal excision.

Wide: Surgical plane is in normal tissue but in the same compartment as the tumour. The recurrence rate is low and is related only to skip lesions in the affected compartment.

Radical: The tumour is removed including affected compartments and there is a minimal risk of local recurrence. (15)

The surgical margin of the tumour post excision, the type of tissue at the margin (e.g. fascia, fat, muscle or skin), whether the invasive margin is infiltrative or pushing, and presence of vascular invasion is an important factor that will guide further treatment and can also be a determining factor for recurrence. (15)

The American joint committee on cancer (AJCC) is used for staging of soft tissue sarcoma It is the benchmark for classifying patients with soft tissue sarcoma, evaluation of prognosis and defining the right treatment approach.(16)

Every patient with a soft-tissue sarcoma will need an individualized treatment plan and the tumour and anatomic characteristics need to be evaluated in a multidisciplinary setting in order to generate an optimal treatment plan. (6) Surgery

is the standard treatment for all patients with adult-type, localised soft tissue sarcomas, and should be performed by a surgeon who has appropriate training in the treatment of sarcoma. Evaluation of the resectability of a tumour is determined by the surgeon in consultation with the Sarcoma multidisciplinary team, and depends on the tumour stage, the anatomical location, and the patient's comorbidities. The primary aim of surgery is to completely excise the tumour with a margin of normal tissue. (6) (9)

Amputation was historically considered the standard of care for patients with STS of the extremity. It essentially eliminated risk of local recurrence, but no difference in overall survival or disease specific survival was observed between the amputation group and non amputated surgical groups.(17)

Advances in treatment, particularly the advent of multimodality treatment, have lowered the amount of amputations needed in the treatment of ESTS and have favoured the use of limb-salvage techniques.18 A study in Johannesburg South African showed that Excision was performed in 107 patients (69.9%). Margins were clear in 16.3% of the 92 specimens for which margins were mentioned in the histological reports, positive in 57.6% and close in 26.1%. (18)

There is strong evidence that adjuvant radiotherapy improves the local control rate in combination with conservative surgery in the treatment of STS of extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins. A local control rate of 90% has been achieved. Improvement is obtained with adjuvant radiotherapy added in the case of intralesional surgery, but the local control rate is somewhat lower.(19) Radiation therapy was commonly used in patients with positive margins to reduce recurrence and achieve a cure. (20)

There is still insufficient data to establish that preoperative radiotherapy is favourable compared to postoperative radiotherapy for local control in patients presenting primarily with large tumours. (19)

In a retrospective review of 231 patients who were referred to Princess Margaret Hospital because of a soft-tissue sarcoma in an extremity, 100 patients were identified who had no metastasis when they were first seen and who had been treated by local resection and adjuvant radiation therapy. Data were collected for each patient for the following variables: age; sex; location of the tumor and its size, grade, depth, and compartmental status; chemotherapy; and dose of radiation. The surgical margins were characterized as positive or negative for histological evidence of disease on the basis of an independent review of the pathological and operative reports by a surgeon and a radiation oncologist who were experienced in the management of sarcoma. Adequacy of the margin of resection was the only variable that was associated with local relapse ($p = 0.0004$). The size of the tumor ($p = 0.0008$) was the major determinant of the risk of systemic disease. (21)

Patients with primary disease had a lower disease-specific mortality in comparison to those first examined for recurrence (25% v 37%, respectively, at 10 years). Size, malignancy grade, depth, histological type, and local recurrence had a statistically significant prognostic effect at multivariable analysis, while microscopically positive surgical margins had not, though a trend in favor of negative margins was observed. However, an extra risk was observed for patients with positive margins after 3 to 5 years (hazard ratio, 1.8 after 5 years v 0.8 before 5 years). In patients treated for a local recurrence, the prognostic impact of positive margins was higher (hazard ratio, 1.6). Positive surgical margins had a weak adverse prognostic effect, which was more pronounced for those patients escaping an early relapse. (22)

The National Cancer Data Base (NCDB) of the American College of Surgeons gather demographic and survival data on 34 of the commonest soft tissue sarcomas, with the overall best prognosis seen in patients diagnosed with dermatofibrosarcoma NOS (97% 2-year, 92% 5-year) and followed closely by well-differentiated liposarcoma (92% 2-year, 84% 5-year). The three sarcomas demonstrating the worst prognosis appear to be rhabdomyosarcoma, NOS (38%, 24%), dedifferentiated chondrosarcoma (43%, 19%), and pleomor-

phic rhabdomyosarcoma, adult type (43%, 27%). (23)

The role of chemotherapy in the treatment of STS is still controversial. A meta-analysis by Pervaiz et al. showed only a marginal efficacy with respect to local recurrence, distant recurrence, overall recurrence and overall survival.(24)

The Soft Tissue and Bone Sarcoma Group of the European Organization on Research and Treatment of Cancer conducted a number of studies of chemotherapy in advanced disease. They showed that doxorubicin had considerable activity and that ifosfamide $5g/m^2$ given over 24 hours was at least as active as cyclophosphamide. Subsequent studies have therefore centered on a combination of doxorubicin and ifosfamide. A large randomized trial showed no significant benefit of doxorubicin/ifosfamide over single-agent doxorubicin, but the doses of doxorubicin were different.(25)

A recent updated metaanalysis in 2008 that includes 1,953 patients recruited in 18 randomized trials favoured chemotherapy arm in terms of odd ratio for local recurrence 0.73 (95% CI :0.56–0.94) and distant/overall recurrence 0.67 (95% CI :0.56–0.82). In contrast to single agent doxorubicin, combination of doxorubicin and ifosfamide was found to improve overall survival with statistical significance. (26) In a retrospective review also of 356 patients with large, high-grade STSs, patients with >10cm, high-grade tumors who were treated with neoadjuvant doxorubicin and ifosfamide had improved disease specific survival at three years when compared to those patients who did not receive therapy (83% versus 62%, respectively).(27)

Patients with histological type that are not sensitive to chemotherapy, usually do not receive treatment with chemotherapy although this pattern may alter as targeted therapies for these tumors are developed and clinical trials examining their activity become available.(17)

Performance status is the most powerful risk factor for early death among patients with advanced soft tissue sarcoma. 11 The performance status were identified by both logistic regression analysis and probability tree analysis in patients captured in the Soft Tissue and Bone Sarcoma Group (STBSG) database (3002 patients). Scores derived from the logistic regression analysis and algorithms derived from probability tree analysis were subsequently validated in an independent study cohort from the French Sarcoma Group (FSG) database (404 patients). The 90-day mortality rate was 8.6 and 4.5% in both cohorts. The logistic regression analysis retained performance status (PS; odds ratio (OR)=3.83 if PS=1, OR=12.00 if PS≥2), presence of liver metastasis (OR=2.37) and rare site metastasis (OR=2.00) as PFs for early death.(28)

Radiation can be administered in the adjuvant or neoadjuvant setting. The risks and benefits of each option have been carefully delineated in a study, which randomized 94 patients to receive 50Gy preoperatively as compared to 66Gy in the postoperative setting. There was no statistically significant difference between the in the rate of local reccurrence and long term survival ($p = 0.71$). (29)

The survival of patients with soft tissue sarcoma depends on the prognostic factors, treatment received and the response to adjuvant therapy. A study showed twenty-six patients had localized disease and 13 patients had metastatic disease at presentation. Twenty-one patients underwent attempted curative resection, 27 received radiotherapy, and 37 received chemotherapy. Median follow-up for surviving patients was 152 months. The overall 5- and 10-year survival rates were 31% and 27%, respectively. Five-year survival rates for patients with tumors less than 5 cm, 5 to 10 cm, and more than 10 cm were 60%, 14%, and 0%, respectively. Patients with localized/locoregional disease at presentation had a 44% 5-year survival rate; there were no 5-year survivors among patients with metastatic disease. Patients who had a complete response to chemotherapy had a 5-year survival rate of 57%, compared with a rate of only 7% for poor responders.(30) Most patients die of metastatic disease, which becomes evident within 2-3 years after the initial diagnosis in 80% of cases.(1)

Between 2006 and 2014, 94 patients with localized STS of the extremity/trunk treated with

preoperative RT and radical resection were identified. Median tumor size was 7.5 cm, and 92% were intermediate/high grade. After a median follow-up of 60 months for surviving patients, 30 patients (32%) recurred, including 5 local recurrence and 26 distal recurrence. The median time to local and distal recurrence was 36.2 months (range 14.4-65.7) and 10.4 months (range 5.2-76.9), respectively, and the 5-year local recurrence-free survival (RFS), distant RFS, and OS was 95, 71, and 76%, respectively.(31)

Management of STS in the developing countries is still a serious dilemma partly because of the late presentation of our patients and largely because of non-availability of some equipment to adequately and appropriately manage these patients. (31)

The management of these patients in Nigeria is complicated by the late presentation with advanced diseases, paucities of treatment facilities for radiation therapy and the low socioeconomic status of patients in this part of the globe. The treatment options of patients with soft tissue sarcoma which include the use of radiation therapy, type of surgical excision done and the chemotherapy used in treating these patients are highlighted in this study. The survival of patients after treatment is difficult to follow up beyond 1 year due to low compliance to follow up care by most patients. Thus the 1 year survival of patients with a statistical test of multi-variable which includes the gender, histologic type (rhabdomyosarcoma versus non rhabdomyosarcoma) and the type of surgical excision performed are evaluated.

MATERIALS AND METHODS

STUDY AREA

The study was conducted in the department of Radiotherapy and Oncology, Usmanu Danfodiyo university teaching hospital, Sokoto state, Nigeria. The hospital is located in the North western part of Nigeria and receives referrals to the Department of Radiotherapy from health institutions of neighbouring states. These include Zamfara, Kebbi, Kano, and Katsina as well as from other parts of the country. These referrals are mainly due to paucity of oncology facilities in those regions.

STUDY DESIGN

This is a five year retrospective study of all patients with soft tissue sarcoma seen in the department of radiotherapy of the Usmanu Danfodiyo university teaching hospital between the periods (1^{st} January 2010 to 31^{st} December 2015).

Data was collected from cases notes, histology reports and treatment cards. Data collected included; socio-demography (age and gender), histological type(rhabdomyosarcoma and non rhabdomyosarcoma), and performance status of the patients at presentation.

Overall survival at one year was calculated from the time of diagnosis to 12 month period.

INCLUSION CRITERIA

1. All patients seen with soft tissue sarcoma.

EXCLUSION CRITERIA

1. All patients with bone sarcoma.
2. All patients without a histological confirmation of soft tissue sarcoma.

DATA ANALYSIS

Data was analyzed using SPSS version 21.0. Qualitative variables will be summarized as tables and charts.

LIMITATION OF THE STUDY

1. It was a retrospective study.
2. The grade of histological diagnosis of patients with soft tissue sarcoma in most histology reports was not documented.
3. Most of the patients could not be properly staged in the retrospective review.
4. The response to chemotherapy could not be ascertained
5. Some patients were lost to follow up within a year after diagnosis.
6. It was not a population based study.

ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Scientific and Health Research Ethics Committee of Usmanu Danfodiyo university teaching hospital, Sokoto before commencement of this study.

RESULTS

A total of 123 patients were reviewed during the study period, of which radiotherapy was given

to treat 86(69.9%) of the patients as seen in Table 1, however most patients had palliative dose of radiotherapy, which constitute 55(64.0%) while 31(36.0%) had radical dose of radiation therapy(Table 2)

Figure 1 shows the type of chemotherapy used by the patients. Several chemotherapy regimens were used in the treatment of patients with rhabdomyosarcoma. A total number of 100 patients had chemotherapy given during their treatment, which were mostly in combination therapy. The most common chemotherapeutic agent used in the treatment was vincristine, which was used in 82% of the patients who had chemotherapy; this was followed by doxorubicin which was administered in 76% patients. The use of ifosfamide was seen in 10% of the patients, while 71% of the patients had cyclophosphamide administered.

Table 4 depicts the survival of patients at one year post diagnosis. There was no significant difference between the survival of the patients and their gender ($p = 0.659$) and histological type (rhabdomyosarcoma and non rhabdomyosarcoma), ($p = 0.075$). However, there was a significant difference between the survival of the patients and the resectability of the type of surgical excision they had ($p = 0.000$)

DISCUSSION

The management of soft tissue sarcoma involves a multidisciplinary team from diagnosis, proper staging, treatment and follow up care. The availability of some of the modalities in low resource countries hinders the proper management of this group of patients. A tissue biopsy is necessary to make a diagnosis of the type of soft tissue sarcoma, grade and differentiation of these tumours.(11) The excision margins of the tumour removed is paramount to guide further treatment and has been shown to affect the prognosis of these patients. (18)

A total of 123 patients were reviewed during the study period of which 69.9% had radiation therapy use. Of those that had radiation therapy, only 36% had radical dose of external beam radiation therapy, while 64% had palliative dose. This is due to the fact that most patients in northern Nigeria present with advanced disease following delayed presentation and radiation therapy is thus given to palliate symptoms which include pain, bleeding, and tumour control. (32) The dearth of radiation therapy facilities is also a contributing factor for those who hitherto had margin status where radical dose would have been curative. Radiation therapy can be used in both neoadjuvant and adjuvant treatment of patients with variable outcomes. A large systematic trial from Canada showed that the progression time and survival is improved by radiation therapy and recommends EBRT for all patients with positive margins post – excision.(33) The use of intensity modulated radiation therapy has been used for patients to deliver a higher dose to the target volume with relatively less dose to the surrounding tissue and organs at risk as compared to 2D conventional radiotherapy technique.(33), (34)

A total of 100 patients had chemotherapy given as a single agent or in combination. Doxorubicin and ifosfamide remain the most effective drugs for the treatment of soft tissue sarcoma.(35) These are used as single agents or in combination with other chemotherapeutic drugs which include vincristine, cyclophosphamide, dacarbazine, vinblastine, doxetaxel, cisplatin, gencitabine. (35) (36) However some types of soft tissue sarcoma are poorly responsive to chemotherapy and other drugs are used in the treatment. Dermatofibrosarcoma protuberance can be treated with imatinib, a tyrosine kinase inhibitor especially for advanced cases.(37) (38) Other targeted therapy can also be used for soft tissue sarcomas. In this study, doxorubicin was used in 76% of the patients who had chemotherapy and ifosfamide was used in only 10%. None of the patients had targeted therapy used during the study period.

The choice of chemotherapy is largely influenced by the high cost and socioeconomic status of the patients, as most of them are not on any health insurance. (32) (39)

The survival of patients with sarcoma of the soft tissue depends on a number of prognostic factors which includes the tumour size, presence of synchronous metastasis, and surgical resection margins. (32) (40) (41) (42)

There was no statistwically significant differ-

Table 1: Patients who received radiation therapy

Radiation therapy	Frequency (%)
Yes	86(69.9)
No	37(30.1)
Total	123(100.0)

Table 2: Radiotherapy intent among the patients

Radiotherapy Intent	Frequency(%)
Radical	31(36.0)
Palliative	55(64.0)
TOTAL	86(100.0)

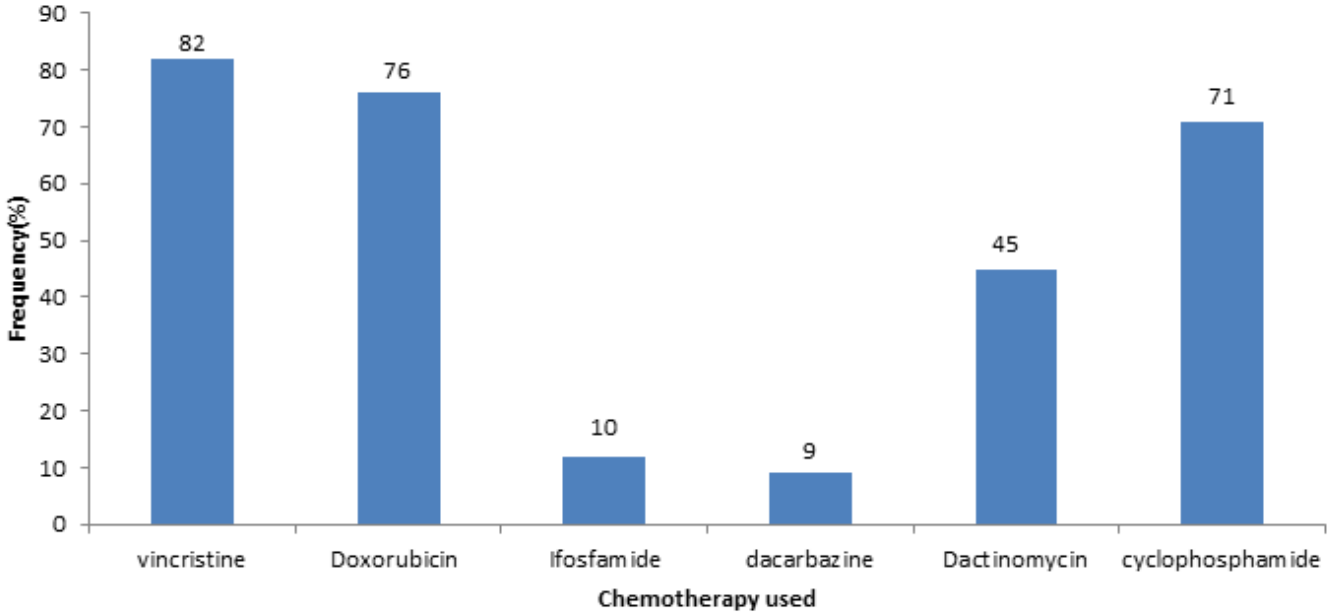

Figure 1: Typeof Chemotherapy used

ence between the age groups, gender and histology types (rhabdomyosarcoma vs. non – rhabdomyosarcoma) of the patients and their overall survival at 1 year (p = 0.659 and p = 0.075 respectively), though some studies have shown gender to be a prognostic factor in patients with soft tissue sarcoma. There was an association between the surgical margin of the tumour and their survival at 1year. Patients who had negative margin had a better survival and those with gross disease (unresectable) had the poorest survival outcome a ta year post diagnosis. This is also seen is other studies where the surgical margin status of the patients was a determining factor on tumour progression, resection and ultimately survival. Patients with non rhabdomyosarcoma soft tissue sarcoma also dependon the histological types; fibrosarcoma and synovial sarcoma have a better prognosis than malignant peripheral nerve sheath tumours and peripheral neuroectodermal tumours. (43)

The performance status of patients with cancer has been shown to be a prognostic factor for survival.(28) This has been clearly established in some hematological malignancies and some solid tumours.(44) (45) This affects the tolerance of pa-

Table 3: Overallsurvival at one year of patients with soft tissue sarcoma

Variable		Survival at 1 year (n = 112)			P value
		Yes	No	Total	
Age group					
	1 – 10	4	5	9	P = 0.173
	11 – 20	10	5	15	
	21-30	21	4	25	
	31-40	14	3	17	
	41-50	14	4	18	
	51-60	12	9	21	
	61-70	3	3	6	
	8.00	1	0	1	
Sex	Male	19	2	21	P = 0.430
	Female	54	19	73	
Histological type	Rhabdomyosarcoma	54	20	74	P = 0,121
	Non Rhabdomyposarcoma	25	13	38	
Perfermance status (ECOG)	0	8	0	8	P = 0.000
	1	47	7	54	
	2	20	8	28	
	3	4	14	18	
	4	0	4	4	
Surgical excision	Radical excision	19	2	21	P = 0.000
	Wide local excision	54	19	73	
	Unresectable	6	12	18	

tients to treatment. There was a significant difference between the performance status of the patients and their survival at a year post diagnosis (p = 0.000). This is in keeping with findings on performance status and survival in literature.(28)

CONCLUSION

The management of patients with soft tissue sarcoma, a rare group of heterogeneous malignancies which can affect different aspect of the body presents a challenge due to compounding socio-economic factors. Surgery is said to be the main treatment of soft tissue sarcoma and a negative margin is essential to achieve a cure for these group of patients. The use of radiation therapy in the treatment of both local and metastatic disease has been documented. Patients who had a positive margin benefit from radiation therapy to the site of surgical excision.

Overall survival at one year abysmal is due to late presentation, and thus with advanced stages

and unresectable disease. This will affect the survival of the patient following treatment. A follow up prospective study to evaluate the response of the patients to the chemotherapy used, tumour control with radiation therapy and longer follow up beyond one year period for survival analysis.

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