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UTERINE SARCOMAS - CORRELATION BETWEEN HISTOLOGICAL TYPES AND OUTCOME

Oncology

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KEYWORDS

INTRODUCTION

Uterine Sarcomas constitute 1% of female genital tract tumors, and 3 – 7% of uterine neoplasms. The WHO has, in 2014, modified the classification of these tumors, the predominant subtypes being Leiomyosarcomas (LMS), Endometrial Stromal Sarcomas (ESS) and Undifferentiated Uterine sarcomas (UUS). High grade ESS (HG ESS) has been reintroduced as a subclass of ESS, distinct from Low grade ESS (LGESS) and UUS. Carcinosarcomas have been excluded from the group of 'sarcomas' and reclassified under "Mixed epithelial mesenchymal tumors". In view of the rarity of these tumors, paucity of data and dependence on case series, we present our experience, to aid further studies.

MATERIALS AND METHODS

This is a retrospective study including all patients diagnosed with uterine sarcomas at KMIO from June 2007 to April 2017. The case files of these patients were retrospectively analysed for demographic profile, clinical characteristics, histopathological features, treatment modalities and outcome. Most patients with stage 4 disease at presentation opted for palliative care, and hence were excluded from our study. Diagnosis was established after histopathological examination of the operative specimen as per WHO criteria. Staging was based on the FIGO 2009 Staging of Uterine Sarcomas. Adjuvant treatment modalities were hormonal therapy, chemo therapy, radiotherapy and chemoradiation. Hormonal therapy was in the form of oral progestins (megesterol acetate, medroxy progesterone actetate or regesterone). Chemotherapy was either anthracycline based (Ifo – Adria, VAdC or CAP) or combination of Gemcetabine plus Docetaxel. External Radiotherapy comprised of 24 fractions of 45 Gy each over 5 weeks, and Bracytherapy was high dose rate (3 sittings of 6 – 7 Gy). Chemoradiotherapy patients received single agent chemotherapy at the time of RT. Follow up was at 3 monthly interval for the first 2 yrs followed by 6 monthly for 2 years and annual thereafter; and included clinical and radiological examinations.

RESULTS

A total of 38 cases were included in our study. Sixteen patients were diagnosed with ESS; 12 had low grade (LG ESS) and 4 had high grade (HG ESS). Fourteen patients had LMS and 6 patients had UUS. There was one case each with Adenosarcoma and rhabdomyosarcoma. Mean age at diagnosis was 46 years. Majority of the patients in our study were premenopausal (58%), with the exception being in the UUS group. Mean BMI was 22; and 86% of the patients were parous. Table 1 shows the clinical characteristics of the patients.

Patient Characteristics	ESS	LMS	UUS	AS	RMS	Total
Total no.	16	14	6	1	1	38
Mean age	43	50	45	60	18	46
Mean BMI	23	21	23	30	21	22
Premenopausal	14 (87%)	5 (35%)	2(33%)	0	1	22 (58%)
Parous	15(93%)	13(92%)	5(83%)	0	0	33 (86%)

The predominant presenting symptom was vaginal bleeding, either in the form of heavy menstrual bleeding or post menopausal bleeding. In the LMS subgroup, the most common symptom noted was abdominal pain, and bleeding disturbances were rare. (Table 2)

Table2 presenting feature by histological subtypes

SYMPTOM	ESS	LMS	UUS	AS	RMS
HMB	11 (69%)	-	2 (33%)	-	1
Abdominal Pain	2(12%)	8 (57%)	1 (16%)	-	-
PMB	2(12%)	4 (28%)	2(33%)	1	-
Mass	1(6%)	-	1 (16%)	-	-
Others	-	2 (14%)	-	-	-

All patients underwent a minimum surgery of TAH. 11 out of 12 pts with LG ESS and pts with other subtypes who had completed their family, underwent BSO also. Retroperitoneal lymphnode dissection was carried out for 14 patients (1 LG ESS, 2 HG ESS, 2 UUS, 8 LMS, 1AS). 6 patients underwent omentectomy. 26 patients were in stage I, 9 patients had stage II disease and 3 were in stage III.

Table 3 shows extent of surgery performed

Surgery	Ess Lg (N=12)	Ess Hg (N=4)	LMS (N=14)	UUS (N=6)	AS (N=1)	RMS (N=1)	Total
Tah Alone	1	1	1	1	-	-	4 (10%)
Tah Bso	11	3	13	5	1	-	33 (86%)
RPLND	1	2	8	2	1	-	14 (36%)
Omentectomy	1	-	2	1	1	-	6 (15%)
Polypectomy	-	-	-	-	-	1	1

Table 4 shows clinicopathological stage of disease

Stage	Ess Lg (N=12)	Ess Hg (N=4)	LMS (N=14)	UUS (N=6)	AS (N=1)	RMS (N=1)	Total
I	10 (83%)	2 (50%)	9 (64%)	4 (67%)	-	1	26 (68%)
II	1(8%)	2 (50%)	4 (28%)	1 (16%)	1	-	9(23%)
III	1(8%)	-	1 (7%)	1 (16%)	-	-	3 (7%)
IV	-	-	-	-	-	-	
Total	12	4	14	6		1	

Adjuvant therapy was individualized based on histological subtype, performance status and stage. A total of 33 patients (86%) received some form of adjuvant therapy. All but 4 LG ESS patients received hormonal therapy. All cases of LMS and majority of HG ESS and UUS were administered chemotherapy. Most commonly followed regimen was anthracycline based. Radiotherapy was sparingly used.

Table 5 shows type of adjuvant therapy received

Adjuvant	Ess Lg	Ess Hg (N=4)	LMS (N=14)	UUS (N=6)	AS(N=1)	Rms (N=1)	Total
Hormones	8 (66%)	-	-	-	-	-	8 (21%)
Chemotherapy	2 (16%)	3 (75%)	12 (86%)	4 (66%)	1	1	23 (61%)
Chemoradiation	-	1 (25%)	-	-	-	-	1 (3%)

Radiotherapy-	-	-	1(16%)	-	-	1 (3%)	
Total	10 (76%)	4 (100%)	12 (86%)	5 (82%)	1	1	33 (86%)

FOLLOW UP

The median follow-up period was 18.5 months (10 – 36 months). A total of 25 events occurred (21 (55%) recurrences, 4(10%) progressions) during the follow up period. 7 patients with LG ESS, 2 patients of HG ESS, 8 patients of LMS and 2 UUS recurred. Median EFI was 19 months (95% CI 0-48). As evident in Table 6, most recurrences were in pelvis. 9 patients had extrapelvic recurrences. 4 patients had progressive disease while on adjuvant therapy. The case of RMS post polypectomy had local recurrence. The three year EFS rate was 40%(Figure1). No significant difference in EFS was observed between the 4 subtypes (Figure 2)

Table 6 shows details of first recurrence following first line therapy

SITE	ESS LG	ESS HG (N=4)	LMS (N=14)	UUS (N=6)	AS(N=1)	RMS (N=1)	TOTAL
PELVIC	6 (50 %)	2 (50%)	2 (14%)	2 (33%)	-	-	12 (32%)
VAULT/LOCAL	1 (8%)	-	1 (7%)	-	-	1	2 (5%)
OMENTAL	1 (8%)	-	2 (14%)	-	-	-	3 (7%)
LUNG	2 (16%)	1 (25%)	2 (14%)	-	-	-	5 (13%)
LIVER	1 (8%)	-	-	-	-	-	1 (3 %)
BRAIN	-	-	1 (7%)	-	-	-	1 (3 %)
MEDIASTINUM-	-	-	1 (7%)	-	-	-	1 (3 %)
TOTAL	8 (66%)	3 (75%)	9 (64%)	2 (33%)	-	1	

Figure 1: Event Free Survival (entire group)

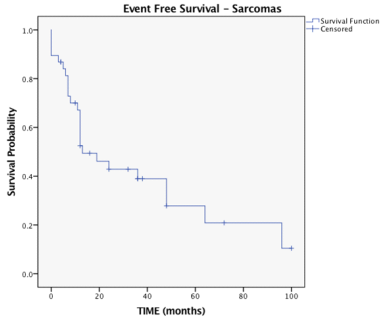
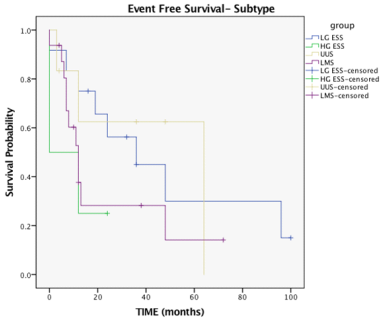


Figure 2 : Event Free Survival (as per subtypes)



Majority of the patients received 2nd line therapy in form of hormones (megesterol, leterozole), chemotherapy or targeted radiation. 19 patients (42% of total and 90% of recurrences) died within 1 year of recurrence. Among LG ESS patients with recurrence, 6 patients (85%) survived > 2yrs from recurrence, while recurrent LMS cases survived only an an average of 4 months (1 – 7 months).

The three-year Overall Survival (OS) for the group was 40 % (Figure 3), the median survival being 25 months (95% CI 11.6-38.3). As shown in Figure 4, the three-year OS for LG ESS, HG ESS, UUS and LMS was 60%, 22%, 50% and 20% respectively. LMS and HG ESS had significant poorer survival (p value 0.03 and 0.02 respectively) than LG ESS and UUS, the latter two having similar prognosis (p value 0.3).

Figure 3 : Three year overall survival of all patients

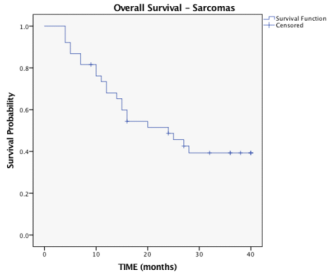
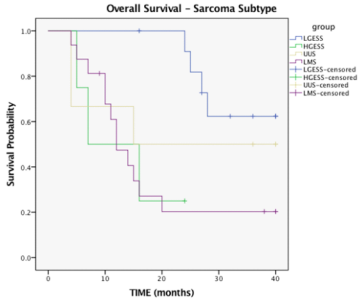


Figure 4: Three year OS according to histopathologic subtype



DISCUSSION

Uterine Sarcomas are rare tumors, accounting for 3 to 7% of uterine neoplasms.1 Carcinosarcomas (40 - 45%) were historically considered the most common type of sarcomas, followed by LMS (35-40%), ESS (15%) and UUS(5%). The most recent WHO 2014 pathological classification, however, has excluded carcinosarcomas from this group.2 We have also chosen patients for our study in accordance with the criteria. In our study, ESS account for the majority of USs, followed by LMS. This could be accounted for by the fact that LMS is frequently operated upon in the periphery as a case of fibroid. Due to the rarity and histolological diversity of these tumors, there is no consensus on prognostic factors and treatment guidelines. Hence, oncologists have to rely upon case series and retrospective data for treatment plans.

The three year OS as well as EFS in our study group was 40%, with a median survival of 25% and median EFS of 19 months. This is comparable with observations made by other authors.3,4 Our study identifies histopathological subtype as a major prognostic factor associated with better overall survival, with better rates for LG ESS as compared to HGESS and LMS. This is despite the fact that there is no significant difference between these groups with respect to EFS. This could be possibly attributed to the better salvagibility seen with second line therapies among LG ESS. The better survival outcome observed with UUS in our study could be due to the restrictive sample size. Stage wise comparison could not be made in view of limited number and the fact that majority patients belonged to stages 1 and 2. Our study has shown an equal propensity towards pelvic and extrapelvic sites in LMS, while the other subtypes most often recurred in the pelvis. This is in concordance with earlier studies. 1,5,6

The role of adjuvant therapy is not well established either. Postoperative hormonal therapy is generally recommended for LG ESS; adjuvant radiation is known to reduce local recurrence without improvement in survival.7 HGESS, ULMS and UUS are treated similarly. Studies have shown no survival benefit with RT in LMS; hence adjuvant RT needs to be individualized for these subtypes.8Adjuvant chemotherapy has been generally used for these aggressive subtypes in view of higher risk of systemic relapse, again with no definitive survival benefits.9,10 If used, the recommended regimes are gemcitabine-docetaxel (preferred for LMS) and anthracycline- doxorubicin based.7 Trabectedin has also emerged as an option for advanced or metastatic LMS following a phase II trial.11

In our study, all patients with aggressive histologies received chemotherapy, predominantly adriamycin- based. Only 3 pateints received radiotherapy. In view of this treatment pattern, no comparison could be made based on adjuvant therapies.

CONCLUSION

Our study is based on the recent WHO classification of uterine sarcomas. The main drawbacks of the study are the small sample size, retrospective pattern and short follow up period. The study reinforces the fact that histopathological type is a major predictive factor in outcome of uterine sarcomas. Our findings justify the the recent reinstatement of the class HG ESS as a separate entity from LGESS and undifferentiated uterine sarcoma. The class of uterine sarcomas continue to be an enigma, and the dismal survival rates with existing therapies urgently warrant further research and multicentric studies to establish uniform treatment guidelines.

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