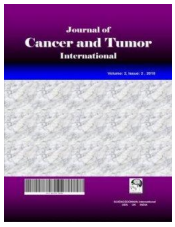

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Uterine Carcinosarcomas versus Leiomyosarcomas: DuaL Institutional Experience from Mansoura and Zagazig Universities

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Carcinosarcomas (CSs) and leiomyosarcomas (LMSs) are rare uterine cancers with high mortality. This study presents a dual institutional experience from two different university teaching hospitals (Mansoura and Zagazig Universities situated in the Delta of the Nile River in Egypt) with regard to the treatment modalities of those two types of uterine cancers aimed at establishing demographics and treatment outcomes.
Patients & Methods: The data from 12 uterine CS and 17 LMS patients treated at the Clinical Oncology Departments of Mansoura and Zagazig Universities from January 2012 to June 2018 were reviewed to evaluate demographics and treatment outcomes.
Results: The mean age of the patients was greater than 50 years. Abnormal uterine bleeding (AUB) was the most common presenting symptom.
Six CS (50%) patients underwent comprehensive surgical staging, while 4 patients underwent total

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abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH&BSO). Conversely, TAH&BSO was performed in 15 patients with LMS (88%).
Adjuvant radiotherapy was given to 6 CS (50%) and 4 LMS (24%) patients. Meanwhile, adjuvant chemotherapy was received by 5 CS (42%) and 8 LMS (47%) patients. Pelvic failure occurred in only the LMS group. Visceral metastasis occurred in both groups, while bone metastasis was encountered in only the CS group. The overall survival at 5 years was 53% and 32% in patients with CS and LMS, respectively.
Conclusion: AUB should be seriously investigated. Both diseases are aggressive despite early presentation and radical multimodality treatment. Local recurrence was reported in only the LMS group. Visceral metastasis occurred in both groups, unlike bone metastasis. New targeted therapies are urgently needed.

Keywords: Abnormal uterine bleeding; uterine leiomyosarcoma; uterine carcinosarcoma.

1. INTRODUCTION

For several decades, there has been a severe deficiency in the process of recording patients' medical histories (particularly for malignant diseases); however, more recently, more attention has been given to this problem. This research presents the experiences of two different university hospitals located in the Delta of the Nile River in Egypt with regard to the management of two rare types of uterine cancers: carcinosarcoma (CS) and leiomyosarcoma (LMS).

The common causes of postmenopausal uterine bleeding are inflammation, polyps, hyperplasia, atrophy, hormonal treatment and cancer [1]. There are two main types of uterine cancer: endometrial carcinoma, which accounts for more than 90% of uterine cancers, and sarcoma [2]. CS is a rare tumour with poor prognosis; it accounts for less than 6% of all uterine malignancies and has been considered a high-risk malignant epithelial tumour, sharing more similarities in clinical scenarios with endometrial carcinoma than with uterine sarcomas [3,4]. According to the 2014 WHO classification of uterine neoplasms, CS is no longer included in recent uterine sarcoma retrospective studies, unlike older literature. On the other hand, uterine leiomyosarcoma (LMS) is the most frequent uterine sarcoma but represents only 2% of uterine cancers [5].

1.1 Aims of This Study

This dual institution retrospective study aims to explore the demographics and treatment outcomes of uterine CS and LMS patients living in the Delta Nile region in the north of Egypt.

2. MATERIALS AND METHODS

We retrospectively reviewed the databases of the Clinical Oncology Departments of Mansoura and Zagazig Universities from January 2012 to June 2018. Data collection was authorized by the institutional review board of the Faculty of Medicine of both Mansoura and Zagazig. Individual patient consent was not required due to the retrospective nature of this study. We excluded patients with other malignancies, poor performance status [The Eastern Cooperative Oncology Group performance status (ECOG) ≥ 3], end-stage renal disease, Child-Pugh C liver cirrhosis, poor cardiac or pulmonary function and patients with missing data regarding their TNM staging.

Patient characteristics that were collected included age, investigations, staging, treatment modalities and treatment outcome. Staging was determined according to the Revised FIGO Staging System of 2009.

Treatment modalities applied by the different physicians and documented in the records were determined through panel discussions. The technique of delineation for conformal radiotherapy was performed according to the RTOG Guidelines. Following treatment, patients were subjected to regular follow-up. Follow-up was performed in the form of a clinical examination plus MRI or CT scan of the abdomen and pelvis every 3 months in the first year, every 6 months in the second year, once in the third year and then every 2 years until death.

Generally, in cases of documented recurrence/progression, the patient was reassessed through panel discussion to decide a suitable salvage treatment.

2.2 Statistical Analysis

Statistical analysis of the data was performed using the SPSS program (Statistical Package for Social Science version 15) to test for statistically significant differences between groups. For quantitative data, a t-test was used to compare between 2 groups. A Chi square test or Fisher's exact test was used when appropriate to examine the relationship between qualitative variables. Overall survival (OS) was described and compared using life tables and the Kaplan-Meier estimator with a log-rank test. Differences were considered statistically significant when $p \leq 0.05$. Overall survival was measured from the date of diagnosis to the date of death from any cause or last follow-up. Treatment failure was considered if there was objective evidence of disease progression locally or distantly or if there was an occurrence of death if there was no progression.

3. RESULTS

The patient & tumour characteristics and initial treatments are shown in Table 1. The mean age was 54.42 (SD ± 12.42) for CS patients and 56.65 (SD ± 13.05) for LMS. AUB was the most common presentation in both groups (83% and 53%, respectively). A complete laboratory profile, biopsy, transvaginal ultrasound, pelvic magnetic resonance imaging (MRI) and computerized axial tomography of the chest and abdomen were performed for all cases at presentation. Six out of 12 CS patients (50%) underwent comprehensive surgical staging, as their preoperative biopsy was conclusive of CS. Comprehensive surgical staging included removal of the uterus, cervix, adnexa, pelvic & para-aortic lymph node tissues and the performance of pelvic washings. Meanwhile, 4 CS patients (33.3%) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH&BSO). One CS patient (8%) underwent palliative uterine resection to stop bleeding, and another patient at stage IV was not operated upon. TAH&BSO was performed in 15 out of 17 patients with LMS (88%), while one patient was surgically treated for a stump sarcoma (6%) and one stage IV patient was not operated upon. Stage I was the most common stage encountered in the 2 diseases (58% and 59% in CS and LMS, respectively). In CS cases, sites of extrauterine tumours at presentation were the cervix in 1 patient, adnexa in 2, pelvic nodes in 1 and omentum in 3 patients. Meanwhile, extracorpus presentations in LMS patients were cervix in 1 patient, omentum in 3, lung in 1 and bone in 1.

The panel decisions followed the policy of personalized treatment encouraging adjuvant treatment application in cases of higher stage, large tumour bulk, lymphovascular invasion or deep muscle infiltration.

A higher percentage of CS patients received adjuvant therapy than the LMS group, as adjuvant radiotherapy (RT) was more frequently applied in the CS group, while adjuvant chemotherapy (CTH) was received by nearly equal percentages of both groups. One CS and 7 LMS patients did not receive any adjuvant treatment.

RT was performed through external conformal radiotherapy, and no brachytherapy was applied. The external RT dose ranged from 45-50 Gy (conventional RT). Adjuvant RT was given to 6 CS patients (50%); 5 cases were stage 1, and 1 case was stage 3. Meanwhile, only 4 LMS patients (24%) received adjuvant RT: 3 patients with stage 1 and 1 patient with stage 2.

On the other hand, adjuvant CTH was given to 5 CS patients (42%); 3 received carboplatin/ifosfamide and 2 received carboplatin/paclitaxel (3 patients had received both adjuvant RT and CTH), while palliative chemotherapy was given to 2 patients (17%). However, adjuvant CTH was given to 8 LMS patients (47%). Six were stage 1, while 2 were stage 2. Five of the 8 LMS patients who received adjuvant CTH had doxorubicin-based regimens, while 3 had taxotere-based regimens (3 patients had received both adjuvant RT and CTH). Palliative CTH was given to 2 stage IV LMS patients (12%).

The median follow-up period was 18 months (range: 2-77). In CS patients, there was no pelvic recurrence/progression. Different sites of non-pelvic recurrence/progression are shown in Table 2. In contrast, 6 women in the group of patients with LMS (35%) developed local pelvic recurrence/progression. Non-pelvic failure sites are also shown in Table 2. Visceral metastasis was reported in both groups, while bony metastasis was encountered in the CS group only.

Upon recurrence/progression, palliative radio-therapy on recurrent pelvic masses or bone metastasis was given to 1 and 3 CS and LMS patients, respectively.

Table 1. Patient, tumour and treatment characteristics in both groups

Characteristics	Group I Uterine carcinosarcoma (n =12)		Group II Uterine leiomyosarcoma (n =17)		p value
	No. of Patients	(%)	No. of Patients	(%)	
Age (years)					
Median (range)	54.5	(23-70)	55.0	(32-85)	0.644
Mean (SD)	54.42	12.041	56.65	13.057	
Presenting symptoms					
Vaginal bleeding	10	(83.3)	9	(52.9)	0.850
Abdominal pain	0	(0.0)	3	(17.6)	
Abdominal mass	2	(16.7)	1	(5.9)	
Vaginal discharge	0	(0.0)	2	(11.8)	
No symptoms	1	(8.3)	2	(11.8)	
Tumour stage					
I	7	(58.3)	10	(58.8)	0.573
II	0	(0.0)	2	(11.8)	
III	2	(16.7)	3	(17.6)	
IV	3	(25.0)	2	(11.8)	
Surgical procedures					
Complete surgical staging	6	(50.0)	0	(0.0)	
Hysterectomy, bilateral SO	4	(33.3)	15	(88.2)	0.008*
Radical surgery for stump	0	(0.0)	1	(5.9)	
Palliative surgery	1	(8.3)	0	(0.0)	
No surgery (biopsy only)	1	(8.3)	1	(5.9)	
Radiotherapy					
Received	6	(50.0)	4	(23.5)	0.236
Not received	6	(50.0)	13	(76.5)	
Chemotherapy					
Received	7	(58.3)	10	(58.8)	0.979
Not received	5	(41.7)	7	(41.2)	

The patients may present with more than one symptom.
*SO: salpingo-oophorectomy; *Significant difference (p ≤ 0.05)*

Table 2. Patterns of recurrence/progression & number of deaths in both groups

	Group I Uterine carcinosarcoma (n =12)		Group II Uterine leiomyosarcoma (n =17)		p value
	No. of Patients	**(%)**	**No. of Patients**	**(%)**	
Recurrence/progression	5	(41.7)	11	(64.7)	0.219
Pelvic	0	(0.0)	6	(35.3)	
Non pelvic					
Lung	2		3		
Liver	2		0		
Bone	1		0		
Omentum	3		6		
Deaths					
Yes	5	(41.7)	11	(64.7)	0.219
No	7	(58.3)	6	(35.3)	

Recurrence may occur in more than one site

Palliative CTH was given to all recurrent and metastatic cases in both groups, the majority of which was taxotere-based. Votrient was used as a second-line chemotherapy in 2 LMS patients. Regarding the response to such palliative CTH, no complete response was achieved, and partial response was achieved in only 2 patients in either group. There were 5 deaths (41.7%) in the group of patients with CS and 11 deaths in the group of patients with LMS (65%). The overall survival at 5 years was 53% in patients with CS and 32% in patients with LMS (hazard ratio of death [HR] = 0.390; 95% confidence interval, 0.085-1.779; p=0.296) (Fig. 1).

Fig. 2 shows the histopathological details of CS, whereas Fig. 3 reveals the details of LMS.

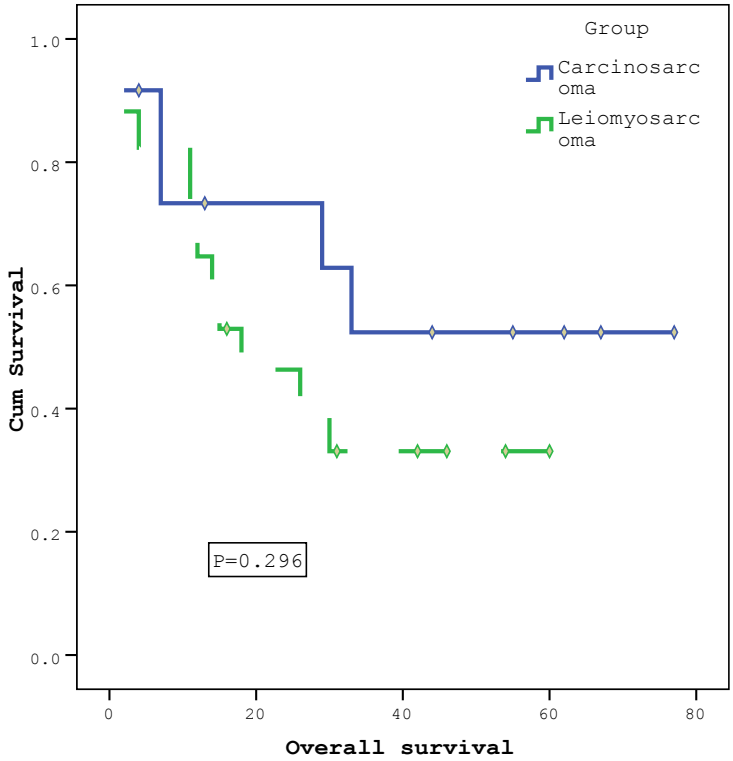

Fig. 1. Overall survival of both carcinosarcoma and leiomyosarcoma patients

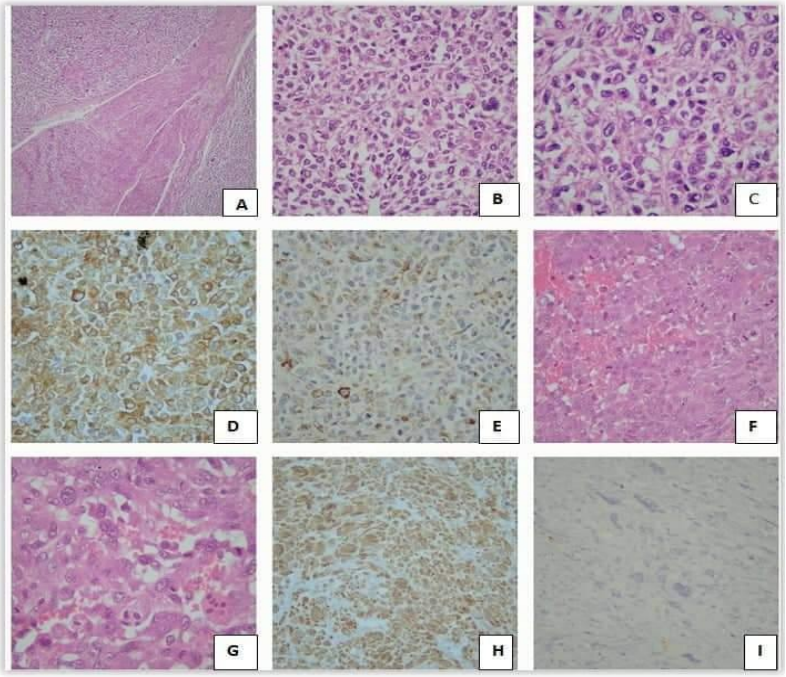

Fig. 2. Carcinosarcoma Carcinosarcoma case with heterologous cartilaginous elements (A, B, C)(H&E 40X). Another carcinosarcoma case with both malignant high grade epithelial and stromal components (D,E)(H&E 200X,400X). Cytokeratin stain highlight epithelial elements (E)(200X). Vimentin highlight the stromal component (G)(200X)

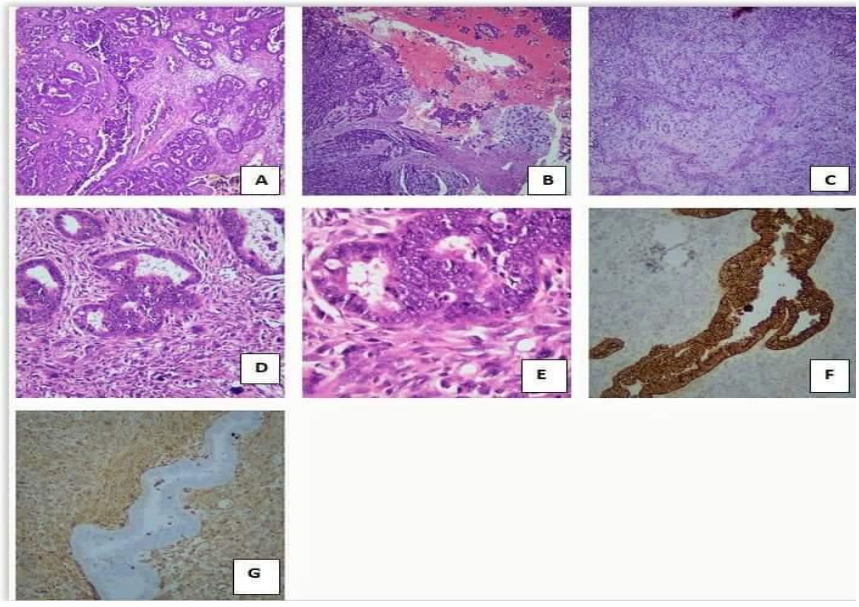

Fig. 3. leiomyosarcoma. Leimyosarcoma show infiltration of myometrial muscle (A). High degree of pleomorphism with frequent mitotic activity (B,C)(H&E 100X,200X). Diffuse positive reaction for smooth muscle actin (D) and focal positive reaction for desmin (E) (100X). Another case of leiomyosarcoma with high degree of atypia and frequent mitosis (F,G)(H&E 100X,200X). Diffuse positive reaction for smooth muscle actin (H)(40X) and negative reaction for CD10 (I)(200X)

4. DISCUSSION

Most of the general population and doctors in our locality are aware of myomas as a neoplastic cause of postmenopausal uterine bleeding; however, knowledge about the incidence of variable types of malignant neoplasms of the uterus may not be clear. The ratio of CS to LMS patients in our cohort was 0.08:1, which is in harmony with the report of Ebner et al. [6], which included 44 patients.

The mean ages of both groups were similar, as were the most common presenting symptoms. This is in agreement with the study by Putikul et al. [7], which comprised 40 patients.

Our treatment plan depended greatly on pelvic MRI imaging. MRI is the main informative radiologic tool used to support transvaginal ultrasound findings in gynaecologic masses. Furthermore, MRI helps differentiate benign from malignant lesions [8].

Stage I was the most common stage at presentation in both diseases. This is in agreement with the literature [7,9]. Comprehensive staging was performed for our CS patients with proven CS pathology in their preoperative biopsy, a policy that is in agreement with Venigalla et al. [10], who performed a retrospective analysis of non-endometrioid types of endometrial carcinoma (7250 patients) with regard to the value of lymphadenectomy. They found that node dissection, especially if the number of nodes resected exceeded 15, was associated with better OS.

Adjuvant RT was received by a larger percentage of patients in the CS group than in the LMS group. Half of our CS patients received adjuvant radiotherapy. An American study by Manzerova et al. [11] analysed CS patients diagnosed between 1999 and 2010 (2342 patients) and treated with surgery with or without adjuvant radiation therapy. Those who received radiotherapy survived longer.

Adjuvant chemotherapy (carboplatin/ifosfamide or carboplatin/paclitaxel) was received by 5 of our CS patients (42%). A recent retrospective study from the Netherlands [12], consisting of 1140 cases of CS, proved that adjuvant treatment, whether chemotherapy, radiotherapy or both, improved OS, especially if lymph node dissection was not performed or if the lymph nodes were infiltrated. Wong et al. [13] analysed 4906 CS patients and found that the impact of both adjuvant chemotherapy and radiotherapy on OS was greater than the impact of each modality alone and better than no adjuvant at all. Unfortunately, we did not have a sufficient number of patients in the present study to assess the impact of adjuvant treatment on survival. The use of either ifosfamide or carboplatin–based adjuvant regimens in our study is in concord with the literature [14,15].

In agreement with the review by Menczer et al., [16] distant metastases were the main mode of recurrence in our CS group. The use of taxotere–based regimens upon developing metastasis in the CS cases in the present study was in concert with the literature. [17] The 5-year survival of our CS patients was 53%, a figure in concord with the reported review by Menczer (50%) [16].

Concerning the LMS group, the standard surgical treatment applied for early stages was TAH&BSO without lymphadenectomy. This is in accordance with the comprehensive reviews by Roberts et al. 18 No laparoscopic resection was performed. Laparoscopy was reported not to be the best choice for that disease [19].

Less than one fourth of our LMS patients received adjuvant RT. Regarding the role of adjuvant radiotherapy following radical surgery, Reed et al. [20] conducted a trial that included 224 uterine sarcoma patients (103 were LMS). In those trials, patients were randomized to either observation or external pelvic RT. No difference between the 2 arms with regard to DFS or OS was found. Analogous results were published by Sorbe and Johanson (62 patients) [21].

Adjuvant chemotherapy was given to 8 LMS out of 17 patients in the present study (47%) and was mainly doxorubicin-based. In 2018, Friedman and Hensley [22] published an interesting review on uterine LMS and concluded that neither adjuvant radiotherapy nor chemotherapy affects the prognosis of uterine-confined, completely resected LMS. The review by Ducie et al. [23] reached the same conclusion; Ducie et al. reported that there was also no proven benefit of chemotherapy for completely resected advanced stages of the disease, although it was commonly considered. They also reported that doxorubicin, with or without other agents, had been chosen as an adjuvant treatment because of its success in achieving a 30% response in measurable disease and that years later, the combination of

gemcitabine/docetaxel had become the favoured protocol, as it achieved response rates that could reach 53%.

Pazopanib was used in 2 of our cases as a second-line regimen after failure of the first-line, docetaxel-based regimen in cases of recurrence. The success of this drug with previously treated, advanced LMS in comparison with other uterine soft tissue tumours has been published [24].

Our 5-year survival for LMS was 32%, which is less than that reported in a remarkable multicentre study by Pellanda et al. (50%) [9]. Would a larger sample size give better survival figure? It is difficult to say at this point.

Local recurrence occurred only in our LMS group. This is consistent with the papers of Sorbe et al. [25] and Tirumani et al. [26]. Sorbe reported a local recurrence incidence of 11% among 322 CS cases, while Tirumani reported 50% local recurrence among 113 uterine LMS cases.

No cases of bone metastasis were reported in the LMS group, while it was reported in the CS group. This is consistent with the literature; bone metastasis was the third highest after abdominal and lung metastasis in metastatic CS patients [27,28]. Bartosch et al. [29] analysed the incidence of different organ metastases in uterine LMS (130 patients), and bone metastasis was observed after lung, cranium, skin and soft tissue metastasis. This means that the chance of bone metastasis is lower with LMS.

Limitations of this study included the limited number of patients, which did not allow for the analysis of the impact of different prognostic factors on survival. Moreover, full surgical staging of all carcinosarcoma cases was not performed, and so it is possible that the staging of some of the cases was not accurate.

5. CONCLUSION

AUB at perimenopausal ages should be seriously investigated. Both uterine CS and LMS groups presented mainly at early stages, but the OS was poor. Radical surgery was the main treatment line in both groups; however, complete surgical staging was practised in the CS group only. Adjuvant treatment was applied more often in the CS group. Local recurrence was reported in the LMS group only, while visceral metastasis was encountered in both groups. Novel targeted therapies and prospective trials are needed to improve the outcome.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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