



## RETROSPECTIVE ANALYSIS OF UTERINE CARCINOSARCOMA FROM A TERTIARY CARE CENTRE IN SOUTH INDIA

### Oncology

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### ABSTRACT

**Background:** Uterine Carcinosarcoma (UCS) is a highly aggressive, rare, biphasic tumour. The study was retrospectively conducted to analyse the clinical profile, treatment and outcomes of uterine carcinosarcoma cases presenting to a tertiary care centre.

**Methods:** In this retrospective study, the clinical characteristics, treatment and outcomes of all patients with uterine carcinosarcoma was evaluated. The study was conducted in a tertiary care hospital, Chennai, India between January 2014 to December 2018. The data was collected from the case records of the eligible participants onto a structured proforma. Demographic, clinical, staging, treatment and its outcomes were the variables of interest for analysis.

**Results:** A total of 18 subjects were included in the final analysis. The mean age of the participants was  $58.72 \pm 8.39$  years. Fourteen (77.78%) participants had BMI <30. Seventeen (94.44%) of study participants were post-menopausal. Ten (55.56%) presented with bleeding, Fifteen (83.33%) with pain and Three (16.67%) with abdominal mass. Sixteen (88.89%) had >50% myometrial invasion. Nine (50%) participants underwent staging LAP/TAH/BSO/omentectomy/lymph node dissection, Four (22.22%) underwent with Radical hysterectomy, Four (22.22%) underwent debulking surgery. Among study population, Six (37.50%) received carboplatin + paclitaxel and Four (22.22%) had adjuvant RT. This study shows overall mortality was 44.44%. Median duration of survival was 16 months (95%CI 3.15 to 28.84) among the study population

**Conclusions:** Uterine carcinosarcoma is a rare tumour, often diagnosed at an advanced stage. Because of its rarity, its profile cannot be generalized to the entire population.

### KEYWORDS

Uterine Carcinosarcoma, Malignant Mixed Müllerian Tumour, Treatment, Chemotherapy.

### INTRODUCTION

Uterine Carcinosarcoma (UCS) also known as Malignant Mixed Mullerian tumor, malignant mesodermal mixed tumor, or metaplastic carcinoma is classified as a high-grade endometrial carcinoma.<sup>2</sup> MMMT is histologically composed of 2 cell types: a carcinoma and a sarcoma.<sup>3, 4</sup> They account for less than 5 percent of all uterine malignancies<sup>8</sup> and have an incidence of less than 2 per 1, 00,000 women per year.<sup>4,5</sup> They contribute to 16.4% of all deaths caused by a uterine malignancy.<sup>6,7</sup> Median age at diagnosis ranges from 62 to 67 years.<sup>9</sup> Classical clinical triad is pain, bleeding, and a rapidly enlarging uterus. Of these, vaginal bleeding is the most common presenting sign for women with carcinosarcoma.<sup>10</sup> **Risk factors, and clinical behaviour more closely with endometrial carcinoma as opposed to uterine sarcomas.** Risk factors are advanced age, obesity, nulliparity and exposure to exogenous estrogen. Furthermore, long term use of tamoxifen after breast cancer has been associated with the development of a uterine carcinosarcoma.<sup>7, 17</sup> They carry a poor prognosis irrespective of the stage at diagnosis and even in early stage disease. Carcinosarcomas have a less favourable outcome compared to other uterine malignancies with 5-year-survival rates between 33% and 39%.<sup>18, 19</sup> 10% of patient present in advanced stage (FIGO stage III/IV).<sup>20</sup>

Only limited studies have been conducted so far which has documented the clinical profiling and treatment outcome of the uterine carcinosarcoma. This study aimed to gain more insight into the clinical profile and treatment outcome of uterine carcinosarcomas in Indian population using hospital-based records of patients referred to a tertiary care hospital.

### METHODS:

The study was retrospective observational study, conducted in the Department of Medical oncology. The study population included, all the confirmed cases of uterine carcinosarcoma by histopathological examination between January 2014 to December 2018. Considering the rarity of the disease, pre study sample size calculation was not done and all the eligible subjects available for the analysis were included in the study.

The data was collected from the case records of the eligible participants onto a structured proforma. Demographic, clinical, staging, treatment and outcomes were the variables of interest for analysis.

Statistical analysis was performed using IBM SPSS statistical

software version 21. Descriptive analysis was done using mean and standard deviation for continuous variables. Categorical variables were summarized by frequency and proportion. Since no hypothesis testing was done, and no statistical test of significance was applied.

### RESULTS:

A total of 18 subjects were included in the final analysis. The mean age of the participants was  $58.72 \pm 8.39$  years. Fourteen (77.78%) had BMI <30. (Table1) There were Seventeen (94.44%) post-menopausal women and only one (5.56%) was pre-menopausal. The parity status showed that only Two (11.11%) were nulliparous. Among the study population Ten (55.56%) presented with bleeding, Fifteen (83.33%) with pain and Three (16.67%) with abdominal mass. Four (50%) participants had Diabetes Mellitus and Four (50%) had DM with Systemic hypertension (Table3). Sixteen (88.89%) had >50% myometrial invasion. Six (33.33%) had Stage I(B), Two (11.11%) with stage IA, Stage IIB and Stage IVB in each, Three (33.33%) with Stage II and 1 (5.56%) was with Stage IIA, Stage IIIA and Stage IIIC. (Table4)

Among the study population Nine (50%) underwent Staging - LAP / TAH / BSO/omentectomy/lymph node dissection, Four (22.22%) underwent radical hysterectomy, Four (22.22%) underwent debulking surgery. Among the study population Six (37.50%) treated with carboplatin + paclitaxel chemotherapy, Four (25%) received adjuvant RT, Two (12.5%) were observed, palliative chemo in Two (12.5%), only one (6.25%) received CDDP + CTX / RT (Table 5) The proportion of overall mortality was 44.44%. Median duration of survival was 16 months (95%CI 3.15 to 28.84) among the study population.

**Table 1: Summary of demographic, menstrual and obstetric parameters of study participants (N=18)**

Parameter	Frequency	Percentages
<b>Age group</b>		
40 to 50	2	11.11%
51 to 60	8	44.44%
61 and above	8	44.44%
<b>BMI</b>		
<30	14	77.78%
≥30	4	22.22%

**Table 2: Descriptive analysis of other parameters in the study population (N=18)**

Parameter	Frequency	Percentages
<b>Menopausalstatus</b>		

Pre	1	5.56%
Post	17	94.44%
<b>Parity(P)</b>		
Nulliparous	2	11.11%
P1	4	22.22%
P3andabove	12	66.67%
<b>Livebirths(L)</b>		
Nil	3	16.7%
1	3	16.7%
Morethan2	12	66.7%
<b>ABORTIONS</b>		
Nil	16	88.9%
1	1	5.6%
2orabove	1	5.6%

**Table 3: Descriptive analysis of clinical presentation and associated co-morbidities the study population (N=18)**

Parameters	Frequency	Percentages
<b>Symptoms</b>		
Bleeding	10	55.56%
Pain	15	83.33%
Abdominal mass	3	16.67%
<b>Co-Morbidities</b>		
DM	4	50.00%
DM / SHT	4	50.00%

**Table 4: Descriptive analysis of HPE type / Grade and stages in the study population (N=18)**

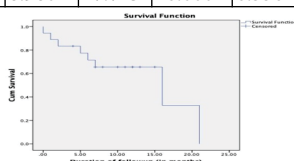
Tumor characteristics	Frequency	Percentages
<b>MYOMATRIALINVASION</b>		
<50%	2	11.11%
>50%	16	88.89%
<b>STAGE</b>		
Stage IA	2	11.11%
Stage IB	6	33.33%
StageII	3	16.67%
Stage IIA	1	5.56%
Stage IIIA	1	5.56%
Stage IIIB	2	11.11%
Stage IIIC	1	5.56%
Stage IVB	2	11.11%

**Table 5: Descriptive analysis of surgery in the study population (N=18)**

Treatment & Outcomes	Frequency	Percentages
<b>SURGERY</b>		
TAH / BSO / OMENTECTOMY	1	5.56%
STAGING - LAP / TAH / BSO	9	50.00%
RADICAL HYSTERECTOMY	4	22.22%
DEBULKING SURGERY	4	22.22%
<b>CHEMOTHERAPY</b>		
CARBO PLATIN + PACLITAXEL	6	37.50%
CDDP + CTX / RT	1	6.25%
OBSERVATION	2	12.50%
PALLIATIVE CHEMO	2	12.50%
ADJUVANT RT	4	25.00%
<b>Mortality</b>		
Alive	10	55.56%
Death	8	44.44%

**Means and Medians for Survival Time**

Mean <sup>†</sup>				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
13.351	2.230	8.980	17.723	16.000	6.556	3.151	28.849



**DISCUSSION:**

Uterinesarcomas are malignant gynaecological tumors with poor prognosis. Carcinosarcoma is a biphasic neoplasm composed of epithelial and mesenchymal elements.<sup>21</sup> Due to the rarity of carcinosarcomas there is no consensus regarding profiling, prognosis and treatment of carcinosarcoma. The current study sought to contribute to determine clinical profile, treatment pattern and outcomes of uterine carcinosarcoma.

Based on the available evidence, surgery is the primary modality of treatment. surgical procedure include, hysterectomy, bilateral salpingo-oophorectomy, omentectomy or omental biopsy, and lymph node dissection and resection of all gross disease. Also adjuvant chemo or radiotherapy has been proven to be associated with increased overall survival and lower recurrence rates irrespective of the stage of disease. But there is no consensus with regard to the optimal mode of adjuvant treatment (chemotherapy or radiation or both) in women with this tumor.<sup>11,22</sup>

One of the recently published systematic review has concluded that, either in the primary treatment/first line therapy of advanced stage metastatic UCS as well as in recurrent disease, adjuvant combination chemotherapy with ifosfamide and paclitaxel, as the most effective treatment regimen.<sup>23</sup> Combination chemotherapy with ifosfamide/cisplatin or ifosfamide/paclitaxel is superior to treatment with ifosfamide alone by recent reviews. Adjuvant paclitaxel and carboplatin adjuvant therapy also has been reported as effective regimen by few studies.<sup>24,25</sup> There are conflicting results with regard to the effect of adjuvant radio-therapy alone on survival.<sup>11</sup>

In the present study, a total of 18 subjects were included. The mean age of the participants was 58.72 ± 8.39. Symptoms at the first visit was bleeding, pain, abdominal mass. Silverberg, S. G., et al.<sup>26</sup> in his study stated that carcinosarcomas typically occurs in postmenopausal women and most women present with abnormal vaginal bleeding and uterine enlargement. At presentation, extrauterine spread is found in one-third of cases. Carcinosarcomas are typically large bulky polypoid masses, filling the uterine cavity, and prolapsing. Similar findings were observed in the study by Cherian, A., et al.<sup>7</sup>, Kurmit, K. C., et al.<sup>27</sup> and Grasso, S., et al.<sup>7</sup>, which was also in accordance to the current study.

In the present study, the treatment with either surgical therapy, radiotherapy and chemotherapy or the combination of treatment. The decision of treatment is individualized based on stage at diagnosis and the general health of the patient. Staging LAP / TAH / BSO/omentectomy/lymph node dissection was the most common surgical treatment performed among half of the study subjects, followed radical hysterectomy or debulking surgery among 22% of the subjects each, with 1 subject undergoing TAH / BSO / Omentectomy. Carbo platin + paclitaxel chemotherapy was the most common adjuvant chemotherapy regimen used among 37.50% of the subjects. Adjuvant RT in 25% of the subjects. Only observation was done in 12.5% of subjects. And only one woman received multimodality treatment (CDDP + CTX / RT). Several studies in the past have reported similar treatment patterns. In the study by Krivak, T. C., et al.<sup>28</sup> in their study of 29 patients with carcinosarcoma, all the patients, except 2 underwent surgical management, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, staging and tumor debulking. Postoperatively, the most common adjuvant therapy given was radiotherapy in 48.18% of patients, chemotherapy in 33.33% of subjects, combined therapy in 1 subject and only observation in 4 subjects. Dickson, E. L., et al.<sup>29</sup> in their study of stage I-III CS, among stage I/II disease 39.9% were treated only by observation (OBS), 17.6% received CT, 19.7% received RT and 22.9% were treated by both CT+RT, following surgery. The risk of mortality was 4 times more with observation, compared to adjuvant CT. CT+RT had significantly better progression free survival compared to CT alone, but overall survival was similar with both treatments. Machida, H., et al.<sup>30</sup> have reported outcomes of 97 women with carcinosarcoma, who underwent surgical staging followed by administration of platinum-based adjuvant chemotherapy in 74 subjects. This study also reported better overall survival of 50.6 months, with adjuvant therapy, as compared to 34.9 months with incomplete multimodal therapy. Galaal, K., et al.<sup>23</sup> in their systematic review have reported, combination chemotherapy with ifosfamide and paclitaxel is associated with lower risk of death compared with ifosfamide alone. In addition, radiotherapy to the abdomen is not associated with improved survival.

In the current study, the proportion of overall mortality was 44.44%.

Median duration of survival was 16 months (95% CI 3.15 to 28.84 months) among the study population. In the study by Krivak, T. C., et al.<sup>28</sup> The median survival of these patients was 31 months, with an overall 5-year survival of 22%. Dave, K. S., et al.<sup>10</sup> have reported a 3-year disease-free survival of 13 patients as 40%, which is considerably lower than the overall mortality in the current study. In study by Anupama, R., et al.<sup>5</sup>, the survival was only 9 months among women with gross extrauterine disease at the time of surgery, but when the disease was confined to the uterus, the survival was 36 months. Similar findings were observed In the study by Grasso, S., et al.<sup>7</sup>, the recurrence free survival was 27 months and overall survival was 103 months. The survival time reported in this study is quite long compared to our study. The variability in the survival rates and duration of survival can be attributed to differences in the population profile, stage of the disease at diagnosis and the treatment modalities across the studies.

The current study had certain limitations. Firstly, this was a case series; thus, the observed association cannot be interpreted as causal inferences. Secondly, the sample size determination was not done and convenience sampling was used from a single centre which reduces the strength of the study. Thirdly, retrospective analysis was done from registries with limited data. All these limitations prevented the study to be generalized to the rest of the population. Even though, the study could not reach any definite conclusions, it contributes largely to the knowledge of existing literature which is rare and also guides future research. Future study must include a prospective study design, with adequate sample on the large scale.

### CONCLUSION:

MMMT is a rare aggressive tumour of the uterus. MMT warrants comprehensive surgical staging followed by adjuvant chemotherapy in patients with both early and advanced stage disease. This study results indicate median duration of survival was 16 month which implies it is an aggressive malignancy, so optimal adjuvant chemotherapy treatment is yet to be established highlighting the need for large multicentric studies on this tumour

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#### DECLARATIONS

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