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### **Uterine Carcinosarcoma: Different Treatment Modalities to a Single Pathology.**

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#### **ABSTRACT**

Uterine carcinosarcomas (UCS), formerly known as malignant mixed Mullerian tumour (MMMT) is one of the rare subtypes of uterine cancer. Thus, it is one of the extremely aggressive tumours. The morbidities and mortalities of carcinosarcoma have increased over the past decades. UCS has a poor prognosis which needs urgency to explore targeted cancer control treatments. In the UK, there are around 9,700 new uterine cancer cases in the UK annually. The incidence rates for uterine cancer in the UK are observed to be higher in females aged 75 to 79. The risk factors for UCS include postmenopausal age, long-term non-contraceptive oestrogen or tamoxifen use, nulliparity, obesity, and African race. Complex hyperplasia with atypia containing the primary lesions is occurred in more than 40% of patients. UCS is of a monoclonal origin evidence of clinical, pathologic, and biological findings. In order to achieve the highest clinical outcome for patients having UCS, preoperative diagnosis, differential diagnosis, and staging are crucial. UCS lesions showed a huge mass filling in the cavity, whereas, some lesions come with small polypoid lesions or endometrial thickening. MRI is considered the first-line modality after lesions are detected. There are several approaches to treat UCS including surgery with or without chemotherapy (single or combined medications), radiotherapy, and targeted therapy. Hence, the high recurrence rate for UCS and the aggressiveness of the disease, surgical interventions with suitable adjuvant treatment seem to be the best way to manage patients having UCS. In this study, we aimed to explore the various treatment modalities of the UCS.

**KEYWORDS:** Chemotherapy; Radiotherapy; Surgery; Treatment; Uterine Carcinosarcoma (UCS).

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## INTRODUCTION

Uterine carcinosarcomas (UCS), formerly known as malignant mixed Mullerian tumour (MMMT) is one of the rare subtypes of uterine cancer accounting for less than 5%. UCS had a relatively lower five-year survival (50%) for early-stage disease to (10-20%) for late-stage<sup>1-3</sup>. Thus, it is one of the extremely aggressive tumours. Usually, patients presented with extrauterine manifestations with or without distant metastases. UCS possesses a high rate of recurrence<sup>4</sup> with different microscopic features, leading to various epithelial and mesenchymal tissues<sup>5</sup>. UCS is a biphasic tumour having both carcinoma and sarcoma components<sup>6-8</sup>. The morbidities and mortalities of carcinosarcoma have increased over the past decades. There was a rapid increase in the incidence of localized stage recently showing improved early detection. UCS has a poor prognosis which needs the urgency of exploring targeted cancer control treatments<sup>9</sup>. The difficulties in UCS treatment arise from its high recurrence rates (37%, 46%, 63%, and 80%) of stages I, II, III, and IV patients, respectively even after receiving such aggressive treatment<sup>10</sup>.

### *Epidemiology*

In the USA, UCS occurred in 4.7% of uterine malignancies<sup>11</sup>. Moreover, in the UK, there are around 9,700 new uterine cancer cases in the UK annually. The incidence rates for uterine cancer in the UK are observed to be higher in females aged 75 to 79<sup>12</sup>. The cancer registration data showed that UCS had 9%- 16.4% of deaths belonging to uterine malignancies<sup>13</sup>, and this fact highlights the aggressive behaviour of the pathology. There is an increase in the incidence of uterine carcinosarcoma, from 2.2 in 2000 to 5.5 in 2016 (per 1,000,000)<sup>14</sup>.

*Risk factors:* Predisposing factors for UCS include postmenopausal age, long-term non-contraceptive oestrogen or tamoxifen use<sup>15,16</sup>, nulliparity, obesity<sup>17</sup>, and African race<sup>17,18</sup>. A considerable number of patients (5–30%) have a history of pelvic irradiation for 14 years<sup>19,20</sup>. In UCS, the median age when the diagnosis is made is around 70 years age<sup>11</sup>.

*Presenting symptoms and clinical signs:* The most common symptom is postmenopausal vaginal bleeding, with or without abdominal pain and (bloody) vaginal discharge<sup>21-23</sup>. On physical examination, the findings revealed an enlarged uterus in 50–95% of cases with a polypoid lesion invading the endocervical canal occurring in 50%<sup>24</sup>.

### *Pathology*

Complex hyperplasia with atypia containing the primary lesions is occurred in more than 40% of patients<sup>14</sup>. UCS accounts for 15% of mortalities caused by malignant tumours of the uterine

corpus and accounts for less than 5% of all uterine malignant tumours<sup>13</sup>. UCS is of a monoclonal origin evidence of clinical, pathologic, and biological findings. These lesions are derived from the Mullerian duct and closely related to high-grade endometrial carcinoma with the driving force to result in sarcomatous transformation (metaplastic carcinoma) according to the stroma or mesenchymal components of endometrial tissues<sup>25-27</sup>. UCS is currently considered a metaplastic carcinoma with mesenchymal dedifferentiation having hybrid cells with epithelial and stromal ultrastructural characteristics<sup>28</sup> with the expression of epithelial markers on mesenchymal cells<sup>29</sup> and high correspondence of molecular markers in epithelial and mesenchymal components<sup>30,31</sup>. The epithelial component is the most important factor in determining the lesions and is measured as having a higher mitotic index<sup>32</sup>, expression of endothelial growth factors<sup>29</sup>, and frequent lymph vascular invasion<sup>30</sup>. Furthermore, in most cases (74–94%) the metastases are epithelial in origin<sup>5,11,29,30,33,34</sup> determined by the epithelial histopathology type<sup>21</sup>. To increase the accuracy of the management of UCS, the characterization of histologic patterns should be assessed carefully<sup>11</sup>.

### UCS Staging

The International Federation of Gynaecology and Obstetrics (FIGO) released the updated 2023 staging of endometrial cancer. The updated features include the various histological types, tumour patterns, and molecular classification owing to achieving the highest level of successful management (Table 1).

**Table 1. (FIGO) Staging of Uterine Corpus Carcinoma and Carcinosarcoma<sup>35</sup>.**

Stage*		Definition
I		Confined to the uterine corpus
	IA	Limited to endometrium or involves less than half of the myometrium
	IB	Invasion of half or more of the myometrium
II		Invasion of the cervical stroma but no extension outside the uterus†
III		Local and/or regional spread of the tumour
	IIIA	Invasion of uterine serosa, adnexa, or both (direct extension or metastasis)
	IIIB	Metastases or direct spread to the vagina and/or spread to the parametria
	IIIC	Metastases to pelvic or para-aortic lymph nodes or to both
	IIIC1	Metastases to pelvic lymph nodes
	IIIC2	Metastases to para-aortic lymph nodes, with or without metastases to pelvic lymph nodes
IV		Involvement of the bladder and/or intestinal mucosa and/or distant metastases
	IVA	Invasion of the bladder, intestinal mucosa, or both
	IVB	Distant metastases, including metastases to the inguinal lymph nodes or intraperitoneal disease.

“Table: FIGO Staging of Uterine Corpus Carcinoma and Carcinosarcoma.” MSD Manual Professional Edition, [www.msmanuals.com/en-gb/professional/multimedia/table/figo-staging-of-uterine-corpor-carcinoma-and-carcinosarcoma](http://www.msmanuals.com/en-gb/professional/multimedia/table/figo-staging-of-uterine-corpor-carcinoma-and-carcinosarcoma). Accessed 22 Sept. 2023.

## **UCS DIAGNOSIS**

In order to achieve the highest clinical outcome of patients having UCS, preoperative diagnosis, differential diagnosis, and staging are crucial. UCS lesions showed a huge mass filling in the cavity, whereas, some lesions come with small polypoid lesions or endometrial thickening. Evaluation of lymph node metastasis is an important factor in management protocol, but it seems to be a bit difficult for imaging staging<sup>36</sup>. Magnetic Resonance Imaging (MRI) and computerized tomography (CT) are common investigations used for differentiation and stage assessment. Imaging scans should identify the location, the size, the blood supply, and the invasiveness pattern of surrounding tissues. The diagnostic accuracy for carcinosarcoma on CT and MRI ranged between 0% and 3.33% and for malignant tumours on CT and MRI ranging between 50% and 83.33%, respectively. MRI is considered the first-line modality after lesions are detected<sup>36</sup>. MRI has an important role in tumour detection, primary staging, and treatment planning of patients having uterine malignancy<sup>37</sup>. MRI is superior to ultrasonography<sup>37</sup> and CT in detecting myometrial invasion<sup>38</sup>.

## **UCS Management**

There are several modalities of the treatment of UCS including surgery in the form of hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection. Surgery is the primary treatment for UCS. Complete cytoreduction should be done to achieve the best overall survival<sup>39,40</sup>. Primary cytoreductive surgery (PCS) includes a total hysterectomy, bilateral salpingo-oophorectomy, cytology, retroperitoneal lymph node sampling or dissection, along with complete resection of the deposit tumours to achieve the minimal residual tumour status (optimal debulking surgery) or gross residual tumour status (suboptimal debulking surgery)<sup>41-44</sup>. Surgery with adjuvant therapies (radiotherapy, chemotherapy, targeted therapy, and some investigated agents) is considered the best treatment approach in order to achieve the best clinical outcome for patients having UCS<sup>45-</sup>  
51.

## **Modalities of the treatment**

Chemotherapy with ifosfamide should be considered in the advanced stage of metastatic UCS as well as an adjuvant combination. Combination chemotherapy with ifosfamide and paclitaxel is

believed to have a lower risk of death in comparison to uses of ifosfamide alone<sup>52</sup>. The worse overall survival in patients having UCS includes advancing age, stage, and the presence of a rhabdomyosarcoma component<sup>53</sup>.

*Surgery and the role of lymph node dissection (LND):* Surgery is a fundamental treatment which is consisting of a total abdominal hysterectomy, bilateral salpingo-oophorectomy with or without omentectomy, and peritoneal washing<sup>54</sup>.

*Radiotherapy:* the common treatment options include vaginal brachytherapy or whole pelvic external beam radiotherapy. Evidence of improved survival with adjuvant radiotherapy is discrete<sup>4</sup>. Several studies concluded adjuvant chemotherapy and radiotherapy after surgery are associated with the better outcome<sup>5,40,55, 56</sup>.

*Chemotherapy:* Evidence suggests that the combination of chemotherapy agents is more effective than a single chemotherapeutic agent<sup>57,58</sup>. Common chemotherapies included ifosfamide-based regimens along with platinum-taxane combinations to lower overall toxicity<sup>59,60</sup>. A significantly improved outcome is associated with chemotherapy after surgery compared to surgery alone<sup>61</sup>. Single agent regimens such as etoposide, doxorubicin, topotecan, cisplatin, paclitaxel and ifosfamide can be used in advanced UCS, with response rates of 7–36%<sup>62</sup>. Cytotoxic doublets or triplets are currently used include carboplatin/paclitaxel, gemcitabine/docetaxel, ifosfamide/cisplatin ifosfamide/paclitaxel, and carboplatin/pegylated liposomal doxorubicin/paclitaxel<sup>4</sup>.

### ***Endometrial Carcinoma Treatment Regimens:***

The current uses of chemotherapies include combination of Carboplatin + paclitaxel, Cisplatin + doxorubicin, Cisplatin + doxorubicin + paclitaxel, Carboplatin + docetaxel, Ifosfamide + paclitaxel (Category 1 for carcinosarcoma), Cisplatin + ifosfamide (for carcinosarcoma).

*Single Therapy:* Cisplatin, Carboplatin, Doxorubicin, Liposomal doxorubicin, Paclitaxel, Topotecan, Bevacizumab, Temsirolimus, Docetaxel (Category 2B), Ifosfamide (for carcinosarcoma)<sup>63</sup>.

*Therapy for Recurrent, Metastatic:* Medroxyprogesterone acetate, amoxifen, Tamoxifen + medroxyprogesterone acetate.

### ***Targeted therapy***

Also, known novel treatments and it has paid attention to, particularly for advanced-stage or recurrent disease. However, studies investigating PARP-1 inhibitors (niraparib<sup>64</sup>, tyrosine kinase inhibitors such as sorafenib<sup>65</sup>, pazopanib<sup>66</sup>, and anti-VEGFs (aflibercept)<sup>67</sup> had no effect on the outcome of the patients.

## CONCLUSION

There are several approaches to treat UCS including surgery with or without chemotherapy (single or combined medications), radiotherapy, and targeted therapy. Hence, the high recurrence rate for UCS and the aggressiveness of the disease, surgical interventions with suitable adjuvant treatment seem to be the best way to manage patients having UCS.

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