The Egyptian Journal of Hospital Medicine (April 2021) Vol. 83, Page 930-934

Uterine Carcinosarcoma: A Plan for Treatment

Sherif E. Sayed,[1] Anwar A. El Shenawy,[2] Waleed M. Mohamed Fadlalla[3]
[1]Departments of Surgical Oncology, Faculty of Medicine, Bany Swif University, Egypt
[2]Department of Surgical Oncology, Faculty of Medicine, Aswan University, Egypt
[3] Department of Surgical Oncology National Cancer Institute, Cairo University, Egypt
***Corresponding author:** Sherif E. Sayed, **Mobile:** (+20)01119335527, Email: sherifelprincesayed@yahoo.com

ABSTRACT

Background: Uterine carcinosarcomas are very aggressive tumors in the womb that are associated with poor prognosis. They represent only less than 5% of uterine tumors and the incidence rate is less than 2 per 100,000 women per year.

Objective: We reviewed diagnosis and treatment of women with uterine carcinosarcoma. To determine if lymphadenectomy, chemotherapy and radiotherapy are associated with decreased recurrence and increased survival. To prove that multimodality therapy including surgery, chemotherapy and radiotherapy are the ideal treatment for this malignancy.

Patients and Methods: The rarity of the tumor made us depend on thirty cases done over 5 years mainly stage 1, 2 and 3 in University of Aswan between 2014 and 2018. We abstracted: histopathology results, survival outcomes from archived medical reports for the qualifying cases and patient demographics. Patient age at surgery and preoperative CA-125 for patient demographics. Histopathological results: cancer stage, depth of myometrial invasion, grade. Treatment data: Surgical details and use of postoperative adjuvant chemotherapy or radiotherapy or both.

Results: Most uterine carcinosarcoma (UCS) patients are candidates for adjuvant chemotherapy combination therapy, but in-depth testing has not been widely used. The high rate of recurrence and poor overall survival indicate an ongoing need for clinical trials specifically. Hazard of death and recurrence decreased with chemotherapy multiagent and vaginal brachytherapy with five years of higher survival and disease free survival. Also lymphadenectomy decreased recurrence and rate of death associated with.

Conclusion: Adjuvant chemotherapy with vaginal brachytherapy with lymphadenectomy were associated with increased survival and decreased recurrence of women with UCS.

Keywords: Multimodality therapy, Plan for treatment, Uterine carcinosarcoma.

INTRODUCTION

Uterine carcinosarcoma (UCS) has been recognized as high-grade endometrial cancer, although it is less than 5 percent of all uterine tumors [(1- 3)]. UCS accounts for 15% of all uterine body malignancy deaths [(4)]. In spite surgery and adjuvant therapy, UCS is aggressive tumors that present with ectopic disease in 60 percent of cases with recurrence in more than 50 percent. UCS are more aggressive tumors than high-grade endometrial carcinoma [(5- 8)].

The high repeat rate and overall survival indicates the need for improvement of management strategies. The ideal treatment is surgery that consists of at least a hysterectomy, salpingectomy, bilateral lymphadenectomy, and pelvic lymph node resection [(8)].

Diagnosis: UCS has a similar appearance to other uterine adenomas. A patient with UCS is often postmenopausal with uterine bleeding, abdominal pain, and an enlarged uterus, although endometrial biopsy usually identifies malignancy, UCS is not always confirmed. UCS may appear on ultrasound as an endometrial mass or as a mass prolapsing from the cervix. Since UCS patients typically have extrauterine disease at presentation, prior to surgery, practitioners may use CT or MRI imaging to help direct patient therapy and surgical planning. However, there is insufficient evidence to conclude that preoperative imaging is useful or cost-effective. CA 125 levels have been measured for patients preoperatively and postoperatively [(9)].

Treatment: As UCS is a very rare tumor, prospective research has been difficult. Most of the treatment-related data available is historical in nature. Although evidence-based algorithms for treatment exist. They are focused on limited, often retrospective studies and may be defective due to the low reproducibility among pathologists of this tumor histology [(10)]. Owing to the aggressive nature of UCS, multimodality therapy is recommended in all but the earliest stage of the disease. The best procedure, however, is still debated.

Surgery: Surgical staging, including bilateral salpingo-oophorectomy hysterectomy, lymphadenectomy and cytoreduction consideration is the initial recommended treatment for UCS, if the patient can withstand surgery. In the case of advanced disease, retroperitoneal lymphadenectomy is critical as part of disease staging for both treatment planning and prognosis, as well as for overall survival, provided that UCS is a high-grade epithelial carcinoma [(11-13)].

Received:4 /1 /2021
Accepted:1/3/2021

Early-stage disease: Hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymph node dissection require complete surgical staging. The Gynaecologic Oncology Group (GOG) has shown that lymph node dissection has upstaged 20 percent of patients with clinical stage I-II UCS [(14)]. Similar to endometrial adenocarcinoma, data support the survival benefit of lymphadenectomy, especially in early stage disease patients [(1, 15)].

Advanced-stage disease: Extrauterine disease also occurs in UCS. While adjuvant therapy will be used in the care of women with advanced stage UCS, surgical cytoreduction should generally be the initial therapy. In the United States, most gynecological oncologists operate on UCS patients with the aim of optimum cytoreduction, but, UCS was not included in endometrial cancer research promoting vigorous surgical cytoreduction for this disease [(11, 12)]. Full resection was correlated with enhanced survival (52.3 months vs 8.6 months, p < 0:0001), indicating that extrapolation of endometrial cancer data could be reasonable [(13)].

Chemotherapy:

Early-stage disease: Given the aggressive nature of UCS, adjuvant therapy may be considered even for patients with the earliest stage, non-myoinvasive disease. Generally speaking, the guidelines for adjuvant chemotherapy are based on retrospective results [(16)].

Advanced-stage disease: Adjuvant chemotherapy is indicated for advanced-stage disease patients [(16)].

Radiotherapy (RT):

Early stage disease: In patients with early-stage disease, adjuvant pelvic RT tends to reduce the risk of pelvic recurrence and may postpone the emergence of distant metastases. A high rate of distant recurrence, however, persists, suggesting the need for systemic therapy [(17)].

Advanced disease: For advanced stage UCS, it does not appear that RT alone is appropriate adjuvant therapy [(17)].

Combination therapy: In general, combination chemotherapy for systemic control, accompanied by consolidation RT consisting of either vaginal brachytherapy or whole pelvic RT for local control purposes, is appropriate for the treatment of women with completely resected early stage (stage I/II disease). Patients with a completely resected node; the addition of tumor-directed radiotherapy to the affected nodal beds, especially in the case of similarly spread endometrial carcinomas, may be considered by providers who use this approach. Following surgical cytoreduction, women with advanced disease may have combination chemotherapy. In such cases, radiation may be used to palliate[(17)].

PATIENTS AND METHODS

The rarity of the tumor made us depend on thirty cases done over 5 years mainly stage 1, 2 and 3 in University of Aswan between March 2014 and August 2018 (10 patients from each stage).

For the qualifying cases, we abstracted from archived medical records: demographics of patients, findings of histopathology results, survival and treatment results.

For patient demographics, patient age at surgery, and preoperative CA-125 level.

Histopathologic findings: Cancer stage, grade and stage based on FIGO, if pelvic and paraaortic lymphadenectomy done.

Treatment data: Surgical details and use of postoperative adjuvant chemotherapy or brachytherapy or both. Disease free survival and overall survival over 5 years were recorded for survival outcomes.

The most common adjuvant radiotherapy was whole-pelvis radiotherapy (WPRT)-based among those who received adjuvant radiotherapy. A taxane-platinum doublet was the most common adjuvant chemotherapy choice among those who received adjuvant chemotherapy.

Ethical approval and written informed consent:

An approval of the study was obtained from Bany Swif University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation.

Statistical analysis

Data were obtained, coded, updated and included in version 20 of the Statistical Package for the Social Sciences (IBM SPSS). Data were described as numbers and percentages for qualitative data, and mean for quantitative data. Chi-square test was used in the comparison between two groups with qualitative data. A significant p-value was considered when it is equal or less than 0.05.

RESULTS

Table 1 displays the patient demographics of the whole sample. The average patient age was 64.6.

Table (1): Patient demographics for carcinosarcoma of uterus

		No	%
Age	<60	10	33.3%
	>60	20	66.7%
CA125	<30	16	53.3%
	>30	14	46.7%
Pelvic lymphadenectomy	Yes	20	66.7%
	No	10	33.3%
Aortic lymphadenectomy	Yes	20	66.7%
	No	10	33.3%
Adjuvant chemotherapy	Yes	18	60.0%
	No	12	40.0%
Adjuvant radiotherapy	Yes	20	66.7%
	No	10	33.3%
Recurrence	Local	10	33.3%
	?	?	?
	Distant	6	20.0%

Table 2 shows five year survival for all patients and show increased survival for <60 year, CA 125, <30, for who did pelvic and paraaortic lymphadenectomy and who took adjuvant chemo- or radiotherapy.

Table (2): Survival (5 years)

		No	%
Age	<60	10	33.3%
	>60	15	50%
CA125	<30	16	53.3%
	>30	9	30%
Pelvic lymphadenectomy	Yes	20	66.6%
	No	5	16.6%
Aortic lymphadenectomy	Yes	20	66.6%
	No	5	16.6%
Adjuvant chemotherapy	Yes	18	60%
	No	7	23.3%
Adjuvant radiotherapy	Yes	20	66.6%
	No	5	16.6%

Table 3 shows recurrence among cases with CA 125 >30, for those of all stages who did have not pelvic or paraaortic lymphadenectomy and those who did not take adjuvant chemo- or radiotherapy for all stages.

Table (3): Comparison between recurrences per stage among patient demographics for carcinosarcoma of uterus

		Stage 1		Stage 2		Stage 3		Chi square test	
		No	%	No	%	No	%	X^2	P value
Age	<60	3	60.0%	3	60.0%	2	33.3%	1.067	0.587
	>60	2	40.0%	2	40.0%	4	66.7%		
CA125	<30	2	40.0%	1	20.0%	2	33.3%	0.485	0.785
	>30	3	60.0%	4	80.0%	4	66.7%		
Pelvic lymphadenectomy	Yes	1	20.0%	1	20.0%	2	33.3%	0.356	0.837
	No	4	80.0%	4	80.0%	4	66.7%		
Aortic lymphadenectomy	Yes	1	20.0%	2	40.0%	2	33.3%	0.485	0.785
	No	4	80.0%	3	60.0%	4	66.7%		
Adjuvant chemotherapy	Yes	1	20.0%	1	20.0%	1	16.7%	0.027	0.986
	No	4	80.0%	4	80.0%	5	83.3%		
Adjuvant radiotherapy	Yes	1	20.0%	1	20.0%	1	16.7%	0.027	0.986
	No	4	80.0%	4	80.0%	5	83.3%		

Table 4 shows local and distant recurrence for those with CA 125 >30, those who did not have pelvic and paraaortic lymphadenectomy and those who did not take adjuvant chemo- or radiotherapy.

Table (4): Comparison between local and distant recurrence among Patient demographics for carcinosarcoma of uterus

		Local		Distant		Chi square test	
		No	%	No	%	X^2	P value
Age	<60	4	40.0%	4	66.7%	1.067	0.302
	>60	6	60.0%	2	33.3%		
CA125	<30	3	30.0%	1	16.7%	0.356	0.551
	>30	7	70.0%	5	83.3%		
Pelvic lymphadenectomy	Yes	1	10.0%	2	33.3%	1.340	0.247
	No	9	90.0%	4	66.7%		
Aortic lymphadenectomy	Yes	2	20.0%	1	16.7%	0.027	0.869
	No	8	80.0%	5	83.3%		
Adjuvant chemotherapy	Yes	1	10.0%	1	16.7%	0.152	0.696
	No	9	90.0%	5	83.3%		
Adjuvant radiotherapy	Yes	1	10.0%	2	33.3%	1.340	0.247
	No	9	90.0%	4	66.7%		

DISCUSSION

The effectiveness of adjuvant therapy for uterine carcinosarcoma has been underestimated in the past, and it is likely that previous available studies have been limited by the unusual presence of this tumor [18, 19]. Our research shows that adjuvant chemotherapy has a role to play in reducing recurrence, but also highlights the significance of chemotherapy for this uterine malignancy, which is highly risky of distant recurrence even in stage I disease, which is in line with **Leath *et al.*** [18].

Primary findings of this research are that uterine carcinosarcoma had a disproportionately high risk of distant recurrence and systemic chemotherapy decreased the incidence of distant recurrence after hysterectomy-based surgical care. Adjuvant chemotherapy is also effective in reducing local recurrence, and if the tumors have two or more risk factors, the addition of radiotherapy to chemotherapy can enhance the local control effects. The basic principle of integrating systemic chemotherapy may also support this result as chemotherapy is effective for local and distant control of recurrence [19].

Indeed, adjuvant radiotherapy in our research and in a pooled study is considered a successful way to minimize local recurrence. In a review of nearly 1500 cases of uterine leiomyosarcoma and endometrial stromal sarcoma, the majority of which was homologous for both forms of sarcoma for uterine carcinosarcoma [20].

Adjuvant chemotherapy is considered as one of the treatment choices for stage IA uterine carcinosarcoma by the existing National Comprehensive Cancer Network (NCCN) management guidelines [21]. As an alternative path to adjuvant therapy, a non-chemotherapy option with tumor-directed radiotherapy is also mentioned. However, in our research compared to a chemotherapy-based counterpart, non-chemotherapy treatment had an elevated risk of both local and distant recurrences. In order to maximize the outcome, adjuvant chemotherapy-based treatment is therefore necessary. Since Internet- based cognitive behavioral therapy (ICBT) has equivalent efficacy with decreased radiation-related adverse effects for vaginal cuff recurrence relative to whole pelvic radiotherapy (WPRT). As indicated by the National Comprehensive Cancer Network (NCCN) guidelines, adding ICBT to chemotherapy could be a safe choice for adjuvant treatment for this disease [22].

Not all women had lymphadenectomy in our study, and only 66.7 percent of women had full pelvic and aortic lymphadenectomy phases. This suggests that a large proportion of women could have had occult or microscopic stag IIIC disease due to the elevated risk of uterine carcinosarcoma of nodal metastasis as with **Cantrell *et al.*** [16] study where 43 percent only had full pelvic and paraaortic lymphadenectomy. Indeed, relative to staged women, unstaged women had increased risks of both local and distant recurrences. Radiotherapy may reduce the local risk of recurrence when lymphadenectomy was not performed, although it did not show statistical significance (10.3% versus 27.3% for no pelvic lymphadenectomy; and 8.5% versus 19.0% for no aortic lymphadenectomy). Our analysis was restricted to a sample size, and further study to investigate this relationship is required.

The strength of this research is the assessment of a sample size of a relatively rare tumor with extensive details on the tumor. In addition similar comparison of treatment results between

chemotherapy/radiotherapy and chemotherapy alone must be carried out. The standard of this research further enriched the confirmation of the diagnosis of uterine carcinosarcoma by the archived histopathology slide analysis by gynecological pathologists.

CONCLUSION

Uterine carcinosarcomas are relatively uncommon but very aggressive tumors that are considered as endometrial cancers of 'grade 3 out of 4' and should be treated as such with full surgical staging and likely cytoreduction, as well as aggressive adjuvant therapy in suitable patients with chemotherapy regimens individualised to the patient and her illness with or without RT. The recognition that UCS is biologically an endometrial cancer with a de-differentiated portion rather than a sarcoma has resulted in new and more tolerable treatment regimens and more focused clinical trials. Targeted treatments should be the subject of future research.

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