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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 he 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[1-3]. 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[4] with different microscopic features, leading to various epithelial and mesenchymal tissues[5]. UCS is a biphasic tumour having both carcinoma and sarcoma components[6-8]. 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[9]. 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[10].

Epidemiology

In the USA, UCS occurred in 4.7% of uterine malignancies[11]. 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[12]. The cancer registration data showed that UCS had 9%- 16.4% of deaths belonging to uterine malignancies[13], 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)[14].

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

Presenting symptoms and clinical signs: The most common symptom is postmenopausal vaginal bleeding, with or without abdominal pain and (bloody) vaginal discharge[21-23]. 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%[24].

Pathology

Complex hyperplasia with atypia containing the primary lesions is occurred in more than 40% of patients[14]. 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[13]. 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[25-27]. UCS is currently considered a metaplastic carcinoma with mesenchymal dedifferentiation having hybrid cells with epithelial and stromal ultrastructural characteristics[28]with the expression of epithelial markers on mesenchymal cells[29] and high correspondence of molecular markers in epithelial and mesenchymal components[30,31]. The epithelial component is the most important factor in determining the lesions and is measured as having a higher mitotic index[32], expression of endothelial growth factors[29], and frequent lymph vascular invasion[30]. Furthermore, in most cases (74–94%) the metastases are epithelial in origin[5,11,29,30,33,34] determined by the epithelial histopathology type[21]. To increase the accuracy of the management of UCS, the characterization of histologic patterns should be assessed carefully[11].

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[35].

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.msdmanuals.com/en-gb/professional/multimedia/table/figo-staging-of-uterine-corpus-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[36]. 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[36]. MRI has an important role in tumour detection, primary staging, and treatment planning of patients having uterine malignancy[37]. MRI is superior to ultrasonography and CT in detecting myometrial invasion[38].

UCSManagement

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[39,40]. 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)[41-44]. 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[45-51].

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[52]. The worse overall survival in patients having UCS includes advancing age, stage, and the presence of a rhabdomyosarcoma component[53].

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[54].

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

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

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)[63].

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[64], tyrosine kinase inhibitors such as sorafenib[65], pazopanib[66], and anti-VEGFs (aflibercept)[67] 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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REFERENCES

1- Cantrell LA, Havrilesky L, Moore DT, O'Malley D, Liotta M, Secord AA, et al. A multi-institutional cohort study of adjuvant therapy in stage I–II uterine carcinosarcoma. Gynecol Oncol. 2012;127(1):22–6.
2- Denschlag D, Thiel FC, Ackermann S, Harter P, Juhasz-Boess I, Mallmann P, et al. Sarcoma of the uterus Guideline of the DGGG (S2k-Level, AWMF Registry No. 015/074, August 2015). GeburtshilfeFrauenheilkd. 2015;75(10):1028–42.
3- Matsuo K, Ross MS, Machida H, Blake EA, Roman LD. Trends of uterine carcinosarcoma in the United States. J Gynecol Oncol. 2018;29(2):e22. doi:10.3802/jgo.2018.29.e22.
4- Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: a review of the literature. Gynecol Oncol. 2015;137(3):581–588. doi:10.1016/ j.ygyno.2015.03.041.
5- Gonzalez Bosquet J Terstriep SA Cliby WA et al. The impact of multi-modal therapy on survival for uterine carcinosarcomas. Gynecologic oncology. 2010:419-423. doi:10.1016/j.ygyno.2009.10.053
6- Gotoh O, Sugiyama Y, Takazawa Y, Kato K, Tanaka N, Omatsu K, et al. Clinically relevant molecular subtypes and genomic alterationindependent differentiation in gynecologic carcinosarcoma. Nat Commun. (2019) 10:4965. doi: 10.1038/s41467-019-12985-x
7- Barker HE, Scott CL. Genomics of gynaecological carcinosarcomas and future treatment options. Semin Cancer Biol. (2020) 61:11020. doi: 10.1016/j.semcancer.2019.10.006

8- Kurman RJ, International Agency for Research on Cancer, World Health Organization. WHO Classification of Tumours of Female Reproductive Organs. 4th ed. Lyon: International Agency for Research on Cancer (2014). 307 p.

9- Chen M He X Yang Q et al. Epidemiology and prediction model of patients with carcinosarcoma in the united states. Frontiers in public health. 2022:1038211-1038211. doi:10.3389/fpubh.2022.1038211

10- Cantrell, L.A.; Blank, S.V.; Duska, L.R. Uterine carcinosarcoma: A review of the literature. Gynecol. Oncol. 2015, 137, 581–588.

11- Matsuo K Takazawa Y Ross MS et al. Significance of histologic pattern of carcinoma and sarcoma components on survival outcomes of uterine carcinosarcoma. 2016:1257-1266. doi:10.1093/annonc/mdw161

12- Uterine Cancer Statistics. Cancer Research UK, 14 May 2015. available from: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Zero.

13- Sherman ME Devesa SS. Analysis of racial differences in incidence survival and mortality for malignant tumors of the uterine corpus. Cancer. 2003:176-186. doi:10.1002/cncr.11484

14- Joo W Yung-Taek O Ha K et al. Trends in gynecologic carcinosarcoma based on analysis of the surveillance epidemiology end result (seer) database. 2023:1188-1188. doi:10.3390/jcm12031188

15- Segev Y Arnon E Siegler E et al. High incidence of carcinosarcoma among patients previously treated with tamoxifen. The israel medical association journal: imaj. 2017:164-167.

16- Curtis RE Freedman DM Sherman ME Fraumeni JF. Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. Journal of the national cancer institute. 2004:70-74.

17- Zelmanowicz A Hildesheim A Sherman ME et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. Gynecologic oncology. 1998:253-257.

18- Brooks SE Zhan M Cote T Baquet CR. Surveillance epidemiology and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecologic oncology. 2004:204-208.

19- Pothuri B Ramondetta L Eifel P et al. Radiation-associated endometrial cancers are prognostically unfavorabletumors: a clinicopathologic comparison with 527 sporadic endometrial cancers. Gynecologic oncology.:948-951. doi:10.1016/j.ygyno.2006.05.039.

20- Doss, L.L., Llorens, A.S., Henriquez, E.M. Carcinosarcoma of the uterus: A 40-year experience from the State of Missouri. Gynecol. Oncol. 1984. 18 (1): 43–53.

21- Artioli G Wabersich J Ludwig K Gardiman MP Borgato L Garbin F. Rare uterine cancer: carcinosarcomas. review from histology to treatment. Critical reviews in oncology / hematology. 2015:98-104. doi:10.1016/j.critrevonc.2014.10.013

22- Callister M Ramondetta LM JhingranA Burke TW Eifel PJ. Malignant mixed mülleriantumors of the uterus: analysis of patterns of failure prognostic factors and treatment outcome. International journal of radiation oncology biology physics. 2004:786-796.

23- Galaal K Kew FM Tam KF et al. Evaluation of prognostic factors and treatment outcomes in uterine carcinosarcoma. European journal of obstetrics and gynecology. 2009:88-92. doi:10.1016/j.ejogrb.2008.12.014.

24- Rani K Jenna -Lynn S . Uterine carcinosarcomas (malignant mixed müllerian tumours): a review with special emphasis on the controversies in management. Obstetrics and gynecology international. 2011. doi:10.1155/2011/470795.

25- Lopez-Garcia MA, Palacios J. Pathologic and molecular features of uterine carcinosarcomas. Semin DiagnPathol2010;27:274–86.

26- McCluggage WG. Uterine carcinosarcomas (malignant mixed mullerian tumors) are metaplastic carcinomas. International journal of gynecological cancer. 2002:687-690. doi:10.1046/j.1525-1438.2002.01151.x

27- Chao KC, Wang PH, Chang CC, Lai CR, Ng HT. Establishment and characterization of a cell line, MT-213-VGH, isolated from a mixed mullerian tumor of the uterus. Acta Cytol 2001;45:683–90.

28- de Brito PA Silverberg SG Orenstein JM . Carcinosarcoma (malignant mixed müllerian (mesodermal) tumor) of the female genital tract: immunohistochemical and ultrastructural analysis of 28 cases. Human pathology.:132-142. doi:10.1016/0046-8177(93)90291-N.

29- George, E., Manivel, J.C., Dehner, L.P., Wick, M.R. Malignant mixed mullerian tumors: an immunohistochemical study of 47 cases, with histogenetic considerations and clinical correlation. Human Pathology. 1991. 22 (3):215–223.

30- de Jong RA Nijman HW Wijbrandi TF Reyners AK Boezen HM Hollema H. Molecular markers and clinical behavior of uterine carcinosarcomas: focus on the epithelial tumor component. Modern pathology : an official journal of the united states and canadian academy of pathology inc. 2011:1368-1379. doi:10.1038/modpathol. 2011.88.

31- Chen X Arend R Hamele-Bena D et al. Uterine carcinosarcomas: clinical histopathologic and immunohistochemical characteristics. International journal of gynecologicalpathology :

official journal of the international society of gynecological pathologists. 2017:412-419. doi:10.1097/PGP.0000000000000346.

32- Emoto M Iwasaki H Ishiguro M et al. Angiogenesis in carcinosarcomas of the uterus: differences in the microvessel density and expression of vascular endothelial growth factor between the epithelial and mesenchymal elements. Human pathology.:1232-1241. doi:10.1016/S0046-8177(99)90043-6

33- Bitterman P Chun B Kurman RJ. The significance of epithelial differentiation in mixed mesodermal tumors of the uterus. a clinicopathologic and immunohistochemical study. The american journal of surgical pathology. 1990:317-328.

34- Sreenan JJ Hart WR. Carcinosarcomas of the female genital tract. a pathologic study of 29 metastatic tumors: further evidence for the dominant role of the epithelial component and the conversion theory of histogenesis. The american journal of surgical pathology. 1995:666-674.

35- "Table: FIGO Staging of Uterine Corpus Carcinoma and Carcinosarcoma." MSD Manual Professional Edition, www.msdmanuals.com/en-gb/professional/multimedia/table/figo-staging-of-uterine-corpus-carcinoma-and-carcinosarcoma. Accessed 22 Sept. 2023.

36- Liming L Wenpeng H Kangkang X et al. Clinical and imaging features of carcinosarcoma of the uterus and cervix. 2021:1-10. doi:10.1186/s13244-021-01084-5

37- Huang Y-T Huang Y-L Ng K-K Lin G. Current status of magnetic resonance imaging in patients with malignant uterine neoplasms: a review. Korean journal of radiology. 2019:18-33. doi:10.3348/kjr.2018.0090

38- Sala E, Rockall AG, Freeman SJ, Mitchell DG, Reinhold C. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. Radiology 2013;266:717-740

39- Vorgias G, Fotiou S. The role of lymphadenectomy in uterine carcinosarcomas (malignant mixed mullerian tumours): a critical literature review. Arch Gynecol Obstet. 2010;282(6):659–664. doi:10.1007/ s00404-010-1649-0.

40- Versluis MAC, Pielsticker C, van der Aa MA, de Bruyn M, Hollema H, Nijman HW. Lymphadenectomy and adjuvant therapy improve survival with uterine carcinosarcoma: a large retrospective cohort Study. Oncology. 2018;95(2):100–108. doi:10.1159/000488531

41- Coleridge SL, Bryant A, Kehoe S, Morrison J. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database Syst Rev 2021;2:CD005343.

42- Huang CY, Chang CM, Wang PH. Dose-dense chemotherapy: a possible high cost-effectiveness treatment for ovarian cancer. Taiwan J Obstet Gynecol 2020;59:351–2.

43- Huang CY, Cheng M, Lee NR, Huang HY, Lee WL, Chang WH, et al. Comparing paclitaxel-carboplatin with paclitaxel-cisplatin as the frontline chemotherapy for patients with FIGO IIIC serous-type tubo-ovarian cancer. Int J Environ Res Public Health 2020;17:2213.

44- Lee WL, Wang PH. Aberrant sialylation in ovarian cancers. J Chin Med Assoc 2020;83:337–44.

45- Gotoh O, Kiyotani K, Chiba T, Sugiyama Y, Takazawa Y, Nemoto K, et al. Immunogenomic landscape of gynecologic carcinosarcoma. Gynecol Oncol 2021;160:547–56.

46- Matsuzaki S, Klar M, Matsuzaki S, Roman LD, Sood AK, Matsuo K. Uterine carcinosarcoma: contemporary clinical summary, molecular updates, and future research opportunity. Gynecol Oncol 2021;160:586–601.

47- Maheshwari U, Rajappa SK, Talwar V, Goel V, Dash PK, Sharma M, et al. Adjuvant chemotherapy in uterine carcinosarcoma: comparison of a doublet and a triplet chemotherapeutic regimen. Indian J Cancer 2021;58:179–84.

48- De Felice F, Lancellotta V, Vicenzi L, Costantini S, Antonacci A, Cerboneschi V, et al. Adjuvant vaginal interventional radiotherapy in early-stage non-endometrioid carcinoma of corpus uteri: a systematic review. J Contemp Brachytherapy 2021;13:231–43.

49- Zhao F, Tan P, Wang C, Ji X, Chen A. Effect of adjuvant therapy on the prognosis in stage I/II uterine carcinosarcoma: a meta analysis. J ObstetGynaecol Res 2021;47:2473–80.

50- Kahramanoglu I, Demirkiran F, Turan H, Bese T, Cebi S, Ilvan S, et al. Adjuvant treatment modalities, prognostic factors, and outcome of the uterine carcinosarcoma. J ObstetGynaecol Can 2021;43:34–42.

51- Vordermark D, Medenwald D, Izaguirre V, Sieker F, Marnitz S. The role of postoperative radiotherapy for carcinosarcoma of the uterus. Cancers (Basel) 2020;12:E3573

52- Galaal K van der Heijden E Godfrey K et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. Cochrane database of systematic reviews. 2013;N2 (20130228). doi:10.1002/14651858.CD006812.pub3

53- Kurnit KC Previs RA Soliman PT et al. Prognostic factors impacting survival in early stage uterine carcinosarcoma. Gynecologic oncology. 2019:31-37. doi:10.1016/j.ygyno.2018.10.034.

54- van der Horst RL van der Hel O Lutgens L et al. The role of multimodal adjuvant therapy for figoi-ii carcinosarcoma of the uterus: a systematic review. Critical reviews in oncology / hematology. 2022. doi:10.1016/j.critrevonc.2022.103701

55- Menczer J. Review of recommended treatment of uterine carcinosarcoma. Curr Treat Options Oncol. 2015;16(11):53. doi:10.1007/s11864-015-0370-4.

56- Cha J Kim YS Park W et al. Clinical significance of radiotherapy in patients with primary uterine carcinosarcoma: a multicenter retrospective study (krog 13-08). Journal of gynecologic oncology. 2016:e58-e58. doi:10.3802/jgo.2016.27.e58.

57- Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25 (5):526–531. doi:10.1200/JCO.2006.06.4907

58- Sutton G, Kauderer J, Carson LF, et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 2005;96(3):630–634. doi:10.1016/j.ygyno.2004.11.022

59- Heinzelmann-Schwarz V, Kind AB, Vetter M, et al. Should MMMT still be treated with adjuvant taxane-based combination chemotherapy? J Cancer Res Clin Oncol. 2020;146(3):695–704. doi:10.1007/s00432-019-03091-y

60- Powell MA, Filiaci VL, Rose PG, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin Oncol. 2010;28 (16):2727–2731. doi:10.1200/JCO.2009.26.8326

61- Cantrell LA Havrilesky L Secord AA et al. A multi-institutional cohort study of adjuvant therapy in stage i-ii uterine carcinosarcoma. Gynecologic oncology. 2012;V127 N1 (2012 10 01): 22-26. doi:10.1016/j.ygyno.2012.06.020.

62- Gurumurthy M Somoye G Cairns M Parkin DE. An update on the management of uterine carcinosarcoma. Obstetrical &gynecological survey. 2011:710-716. doi:10.1097/OGX.0b013e31823e0c44.

63- Dandamudi RK Aslam S Walji N El-Modir A Fernando I. Chemotherapy for uterine carcinosarcoma with carboplatin ifosfamide and mesna. Anticancer research. 2015:4841-4847.

64- Aghajanian C Sill MW Secord AA Powell MA Steinhoff M. Iniparib plus paclitaxel and carboplatin as initial treatment of advanced or recurrent uterine carcinosarcoma: a gynecologic oncology group study. Gynecologic oncology. 2012:424-427. doi:10.1016/j.ygyno.2012.05.024

65- Nimeiri HS Oza AM Morgan RJ et al. A phase ii study of sorafenib in advanced uterine carcinoma/carcinosarcoma: a trial of the chicagopmh and california phase ii consortia. Gynecologic oncology. 2010:37-40. doi:10.1016/j.ygyno.2010.01.013.

66- Campos SM Brady WE Moxley KM et al. A phase ii evaluation of pazopanib in the treatment of recurrent or persistent carcinosarcoma of the uterus: a gynecologic oncology group study. Gynecologic oncology. 2014:537-541. doi:10.1016/j.ygyno.2014.02.036.

67- Mackay HJ Buckanovich RJ Hirte H et al. A phase ii study single agent of aflibercept (vegf trap) in patients with recurrent or metastatic gynecologic carcinosarcomas and uterine leiomyosarcoma. a trial of the princess margaret hospital chicago and california cancer phase ii consortia. Gynecologic oncology. 2012:136-140. doi:10.1016/j.ygyno.2011.11.042.