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Carcinosarcoma of uterus: a review

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ABSTRACT

Carcinosarcoma of the uterus is an aggressive, rare biphasic neoplasm composed of malignant epithelial and mesenchymal elements believed to arise from a monoclonal origin. The principal treatment in early/locally-advanced carcinosarcoma is surgery. Because of its aggressiveness, it generally presents distant metastases at diagnosis. Adjuvant radiotherapy and chemotherapy have uncertain effect. Chemotherapy alone or associated with radiotherapy seems to improve disease free survival (DFS) and overall survival (OS) in stage III and IV UCS. No advantages in OS and DFS have been shown with radiotherapy alone. The present review summarizes and analyzes the most important features about this type of gynaecological cancer.

Keywords: Carcinosarcoma of uterus, MMMT uterus, Radiation therapy, Monoclonal

INTRODUCTION

A malignant mixed Mullerian tumour (MMMT), also termed uterine carcinosarcoma, is an extremely rare tumour comprising less than 3% of uterine neoplasms. It is highly malignant tumor with poor prognosis of post menopausal age group. However, it may occur in premenopausal women as well. [1],[2]

We conducted Google scholar and PubMed search of literature using phrase words, carcinosarcoma of uterus and malignant mixed mullerian tumors. References of all publication were also searched. All relevant publications were collected, reviewed, analyzed and summarized in this paper.

EPIDEMIOLOGY AND ETIOLOGY

Carcinosarcoma usually arises from uterus but may rarely arises in ovary, fallopian tube, cervix. 3],[4],[5]. The incidence of carcinosarcoma is about 1.5- 3% of all uterine malignancies. The median age of diagnosis is 62 67 years. [6] The incidence usually begins to increase after 50 years of age. Carcinosarcoma is more often in black as compared to white (23% versus 15%).[7]

Factors mainly contributing to development of carcinosarcoma are obesity, nulliparity, exposure to human papilloma virus, use of Tamoxifen, and prior irradiation to pelvis.[8],[9] Kloos et al had shown the causal role of a prolonged exposure to tamoxifen on the subsequent development of uterine carcinosarcoma.[9]

Studies have shown that 5%–30% of patients with carcinosarcoma have a history of pelvic irradiation. These neoplasms will often be diagnosed after a latent period of 14 years after irradiation. [10]

PATHOLOGY

Carcinosarcomas are composed of two histological subtypes which are classified based on the appearance of the sarcomatous component. It is currently believed that carcinosarcomas have a monoclonal origin from a common multidirectional progenitor stem cell. Though epithelial markers are expressed in more than 60% of the sarcomatous component, mesenchymal marker expression is rare in the carcinomatous element.[11] Clinical, pathological, and molecular observations suggest that these neoplasms are derived from the Mullerian epithelium's single stem cells, with metaplasia or dedifferentiation resulting in the sarcomatous elements.[11]

Grossly, the endometrial carcinosarcomas show sessile or polypoid, bulky often hemorrhagic or gritty mass (ranging 2 – 20 cm) usually filling the endometrial cavity or may protrude through the cervical os and fills the vaginal vault.[12] In some instances the tumor infiltrates deeply to myometrium of the uterus that leads to expansion of the walls. Microscopically, carcinosarcoma has both the epithelial and mesenchymal elements.[13] The malignant epithelial elements are typically an adenocarcinoma of endometriod type but serous, mucinous, clear cell, squamous cell and differentiated carcinomas are not rare. The mesenchymal element may be (a) homologous, containing cells native to the uterus including stromal sarcoma, fibrosarcoma, undifferentiated sarcoma, or leiomyosarcoma (2%) or (b) heterologous with mixed components including rhabdomyosarcoma (18%), chondrosarcoma (10%), osteosarcoma (5%), or liposarcoma (1%).[14],[15] Carcinosarcomas express epithelial (epithelial membrane antigen (EMA), pancytokeratin) and stromal lineage markers in relation to their histological appearances such as desmin in muscle differentiation or S100 in areas with chondroid or lipomatous differentiation.

CLINICAL PRESENTATION

Usually patients are post menopausal presenting with irregular bleeding or discharge per vaginal may be associated with a protuberant fleshy mass from the cervix.[16],[17] The discharge may be bloody or watery. Sometimes patient may present with non specific symptoms like weakness, abdominal swelling, pain or abdominal mass and sometime increased abdominal girth. In advanced stages, the patient could complain of urinary tract or gastrointestinal symptoms.

Metastatic pattern in carcinosarcoma depends upon the dominant element (epithelial vs mesenchymal) in histopathology. Studies have shown that the carcinomatous component has a potential for lymphatic spread to pelvic and paraaortic lymph node as compared to sarcoma which metastasize to the peritoneal cavity or hematogenously to the lungs. In sarcoma, lymph node metastasis is very uncommon. In a study Bitterman et al. found that carcinosarcoma metastasize mainly to lymph nodes, ovaries, fallopian tubes and omentum and uncommonly to parametrium, bowels, liver and tonsils and concluded that epithelial component of these tumors invades lymphatic/vascular spaces and metastasizes, whereas the spindle cell component has limited metastatic potential.[18] Similar finding were supported by other studies also.[19],[20]

A simple working classification for the staging of carcinosarcoma tumours is as folows: stage I tumours are confined to the corpus uteri, stage II tumours involves both the corpus and the cervix, stage III tumours are limited the lesser pelvis, and stage IV tumours have extrapelvic extension.

ROLE OF IMAGING

The diagnosis of carcinosarcoma is usually made post operatively after histopathology and IHC studies. But with the use of imaging, Preoperative diagnosis of uterine carcinosarcoma can be made which facilitate the planning of appropriate surgical management with adjuvant therapy.

Current surveillance strategy, consisting of physical examinations and conventional imaging modalities, such as CT and/or MRI, has limited sensitivity and cannot detect recurrences consistently, especially in asymptomatic patients. [21]

Magnetic Resonance Imaging (MRI), Studies have shown that these tumors are usually sharply demarcated. [22] Bharwani et al. had shown that 76% of tumours were well defined with 61% having irregular margins. On T1-weighted images, the majority of uterine carcinosarcomas were isointense to the myometrium (76%) and the endometrium (71%) compared with endometrial carcinoma that was isointense to both these elements in 59% of cases. T2-weighted images found hyperintensity of uterine carcinosarcomas to the myometrium (92%) and hypointensity (55%) or isointensity (41%) to the endometrium, a finding that is highly comparable to endometrial carcinoma (97% hyperintense to myometrium, 23% isointense, and 68% hypointense to endometrium).[23]

In another study Takeuchi et al demonstrated , that there is relatively high mean ADC , low choline concentration and high lipid peak in carcinosarcoma due to intra-tumoral heterogeneity with necrosis and epithelial cystic components.[24]

PET/CT may be used for the diagnosis of uterine sarcoma and the differentiation of malignant and benign lesions. Positron emission tomography/CT has shown high sensitivity of 87.5% and specificity of 97.5% for detecting disease in asymptomatic patients, and 92.9% and 100%, respectively for patients suspected of recurrence on CT.[21] Several studies have demonstrated that the sarcoma fluorodeoxyglucose (FDG) uptake level can be used to evaluate tumor response to treatment as FDG uptake is related to disease recurrence and to survival of patients with sarcomas.[25] The use of PET for uterine sarcoma can be extended with the use of other tracers such as C-11 choline, C-11 methionine, C-11 tyrosine, F-18 fluorotyrosine and F-18 fluorothymidine, all of which characterize tumor biology other than glucose metabolism.[21] PET is beneficial in excluding falsely inoperable disease as staged by MRI or CT and in making a decision on palliation for better quality-of-life.[26]

MANAGEMENT

Surgery is the primary treatment for all patients with uterine sarcoma; however, high rates of relapse and metastases postoperatively necessitate effective adjuvant therapies.[27] Therefore , multimodality treatment has been suggested, with results indicating that surgery followed by a combination of both chemotherapy and radiation therapy yields a significantly longer median disease-specific survival (DSS) of 31 months versus surgery alone (DSS = 3 months), radiation therapy alone (DSS = 15 months), or chemotherapy alone (DSS = 14 months).[28] These findings are further supported by other studies also.[29]

Surgery

The current surgical practice recommended for uterine carcinosarcoma is surgical staging with TAH with BSO, pelvic lymphadenectomy, and para-aortic lymph-node sampling with peritoneal washings. [30] For patients with advanced disease, cytoreduction surgery followed by adjuvant treatment is recommended.

The role of pelvic and para-aortic lymph-node sampling, the method, technique of dissection, and the optimal number of lymph nodes to be sampled remains undetermined. [31], [32] Nemani et al reported a median survival of 54 months in patients who underwent a lymphadenectomy compared to 25 months in those that did not. [31]

Radiotherapy

The indication for adjuvant radiation therapy depends on post‑operative residual disease or surgical inaccessible sites as well as lymph node status. It is well established that radiation therapy improve loco-regional control but demonstration of a survival advantage remains uncertain.[30] Callister et al. (n = 300) demonstrated that adjuvant radiation therapy is associated with lower pelvic recurrence rate ; however, no statistically significant overall survival benefit was found.[27] Similar results were also shown by Sartori et al. [33]

In contrast, other studies have demonstrated a prolonged OS treated with adjuvant radiotherapy. [31], [34], [35] In a study by Clayton Smith et al. (n = 300), radiation therapy increased 5-year survival rates from 33.1% (patients not receiving adjuvant radiation therapy) to 42.4% (patients receiving adjuvant therapy. Multivariant analysis further reported adjuvant radiation therapy conferred benefits for both overall and uterine-specific survival in women stages I–IV, with the greatest impact on Stage IV disease. [34] In another study Nemani et al. (n = 1697) demonstrated a median survival increase from 23 months to 29 months in patients who had not undergone lymph-

node dissection with a 5-year OS increase from 33.4% to 35.8%.[31]

Radiation therapy has been most commonly used as an treatment modality to reduce pelvic failure. It has been advocated that radiation therapy to be given in doses of 5000-6000 cGy to the pelvis. Some authors also recommend intravaginal brachytherapy to deliver a boost to the vaginal cuff. Preoperative radiation is infrequently used and typically given in patients with bulky cervical involvement or parametrial extension.

Chemotherapy

Despite surgical extirpation of the primary tumour, sites of failure occur in both pelvic and extrapelvic regions. Pelvic radiation usually reduces local recurrence. Extrapelvic recurrence/relapse is common with hematogenous, transcoelomic, and lymphatic spread of the tumour; therefore, chemotherapy has a definitive role to minimize both local and distal failure. [36] Identification of effective chemotherapeutic agents to treat patients with uterine carcinosarcomas is essential due to such high incidence of disseminated disease at presentation.

The Gynecologic Oncology Group compared whole abdomen–pelvic irradiation to three cycles of combination chemotherapy with cisplatin and ifosfamide in 206 eligible patients with stages I–IV and very limited residual disease after surgery. The estimated death rate was 29% lower with chemotherapy compared with radiation treatment, but this result did not reach statistical significance. [37]

The most active single agents are cisplatin and ifosfamide, achieving responses in first line from 19% to 42% and in second line in 18% of patients.[38], [39], [40], [41], [42] Paclitaxel and topotecan have been studied in second-line therapy with response rates of 18% and 10%, respectively. [43],[44]

Combination chemotherapy was compared with single-agent treatment in two randomized phase III trials. Cisplatin–ifosfamide resulted in a substantially higher response rate of 54% compared with 36% with ifosfamide alone. Progression-free survival was also substantially longer, but no overall survival benefit was seen.[45] The combination of paclitaxel and ifosfamide achieved a substantially higher response rate than ifosfamide alone (45% versus 29%) with manageable side effects. [46]

In conclusion, the combination of paclitaxel and ifosfamide leads to substantially better response rate and overall survival compared with ifosfamide alone in patients with advanced carcinosarcomas.

The recent advances in the biology of uterine sarcoma made possible to define the treatment target. These are tyrosine kinase receptors and vascular endothelial growth factors. Some investigators have studied the biologic agents. Emoto et al., demonstrated the inhibition of vascular endothelial growth factor (VEGF) expressing malignant mixed tumor line by TNP‐470 (an angiogenesis inhibitor).[47]

RECURRENCE AND METASTASIS

Recurrences in uterine carcinosarcomas occur in over half of patients after primary surgical and adjuvant therapy.[15] Even in early-stage disease, rates of recurrence are reported between 47%–64% and up to 80% of these will be associated with distant metastases.[48] Specific factors that increase the risk of recurrence include patient age, adnexal spread, metastases to the lymph nodes, tumour size, lymphatic-vascular space involvement, histologic grade, cell type, peritoneal cytologic findings, and the depth of invasion of the primary tumour. Interestingly, on multivariate analysis, only adnexal spread, lymph-node metastases, sarcoma cell type, and sarcomatous grade were positive predictors of recurrence. [15]

PROGNOSIS

Carcinosarcomas behave aggressively and have a poor overall prognosis, considerably worse than high-grade endometrial carcinoma, even after other important prognostic variables such as stage, depth of myometrial invasion, and lymphatic and vascular space invasion are taken into account [49]. The 5-year survival ranges from 60%-75% for uterine-confined disease, 40%-60% for early-stage disease (I and II), and 15%-30% for late-stage disease with a median survival of less than 2 years. [50], [51]

CONCLUSION

The carcinosarcomas are a biphasic malignancy consists of malignant epithelial and mesenchymal

components. It is a rare, highly aggressive, rapidly progressing neoplasm associated with a poor prognosis that has not significantly improved in the past thirty years despite advances in imaging and adjuvant therapies. This tumor warrants compressive surgical staging to assess tumor dissemination followed by adjuvant treatment in form of radiation therapy and /or chemotherapy in both early and advanced stage diseases.

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