

Carcinosarcoma of ovary, its histopathological, management and prognostic analysis with review of literature

Abstract

Carcinosarcoma is a mixed malignant biphasic tumour with rare entity and comprises of both epithelial and mesenchymatous components. Primary ovarian carcinosarcoma is a rare neoplasm with number of cases reported in the literature in hundreds and accounts for less than 1% of all ovarian tumours. These tumours are usually diagnosed at an older age and at an advanced stage. It has aggressive clinical behaviour and survival depends on stage at presentation. Radiological imaging findings cannot differentiate carcinosarcomas from other ovarian cancers. Diagnosis is based upon histological findings. Cytoreductive debulking surgery is a crucial part in the treatment of carcinosarcoma of ovary. The role of adjuvant chemotherapy regimen is still controversial. Combination chemotherapy with taxane and platinum based regimen or ifosfamide and platinum based regimen are considered as adjuvant treatment. Despite aggressive treatment modalities such as surgery and chemotherapy, there is poor outcome. Response to therapy and overall survival are poor in comparison to epithelial ovarian malignancies. But due to rarity of the disease, such poor prognosis needs collaboration of studies with molecular analysis to obtain new therapeutic guidelines to improve survival of the patients.

Keywords: Carcinosarcoma, chemotherapy, cytoreductive surgery, heterologous elements, prognosis, ovary.

Introduction

Ovarian cancer is the second most common gynaecologic cancer and is one of the most lethal female malignancies [1]. Sarcomas are rare malignancies of ovary. Carcinosarcoma, leiomyosarcoma, rhabdomyosarcoma, fibromyosarcomas and angiomyosarcomas are the possible different type of sarcomas in ovary [2]. Carcinosarcoma is the most frequent subgroup among these. Ovarian carcinosarcoma is a rare subtype of ovarian cancer with an aggressive behaviour and poor prognosis. Survival of ovarian carcinosarcoma in both early and late stage is inferior to serous ovarian carcinomas [3]. In female genital tract it is commonly seen in uterus and ovarian pathology is a rare entity. Peritoneal, fallopian tubes, cervical and vaginal carcinosarcoma are also rarely seen [4]. Ovarian carcinosarcoma is also known as malignant mixed mullerian tumours (MMMT). Majorities occur in postmenopausal women and only 10% of cases occur only in younger women [5]. **Obesity, nulliparity, exogenous oestrogen and long term tamoxifen use are the possible risk factors for MMMTs [6].** There are no standard guidelines for the treatment. The data published in the

literature are only retrospective reviews and few institutions are able to do prospective studies. According to some studies, optimal cytoreductive surgery followed by adjuvant chemotherapy may be **associate** with improved survival [7-10]. The purpose of the review is to compare and give a **a** extensive idea from the published data regarding management and prognosis of the disease.

Incidence

Ovarian cancer is the fifth leading cause of cancer related death among women and 22,280 cases with 15,500 deaths **reported** in 2012 [11]. **Majorities** are epithelial types with serous subtype being the most common. Carcinosarcoma is a rare histological subtype of ovarian malignancy and is diagnosed in 1-4% among all ovarian cancer survivors [12-17]. Carcinosarcoma of the ovary is nearly three times less prevalent than that of uterus [18]. **Majorities** are seen in Caucasian and present at advanced stages [7]. Fewer than 400 cases have been reported in the literature [15]. **Carcinosarcoma predominantly occur in postmenopausal women with low parity [19]** and the mean age of presentation is 65 years [15]. Pelvic irradiation may increase the incidence of MMMT [20].

Histogenesis

A recent study shows a monoclonal theory of histogenesis in ovarian carcinosarcomas. According to this, metaplastic transformation of the epithelial component causes tumourigenesis resulting in formation of sarcomatous component [21]. But, high rate of recurrence in MMMT of ovary treated with platinum based regimen **suggesting** insufficiency of the theory. Further study on molecular characteristics is necessary to develop knowledge regarding specific targeted therapies to increase survival outcome.

Three theories try to explain the histogenesis of MMMTs [5]:

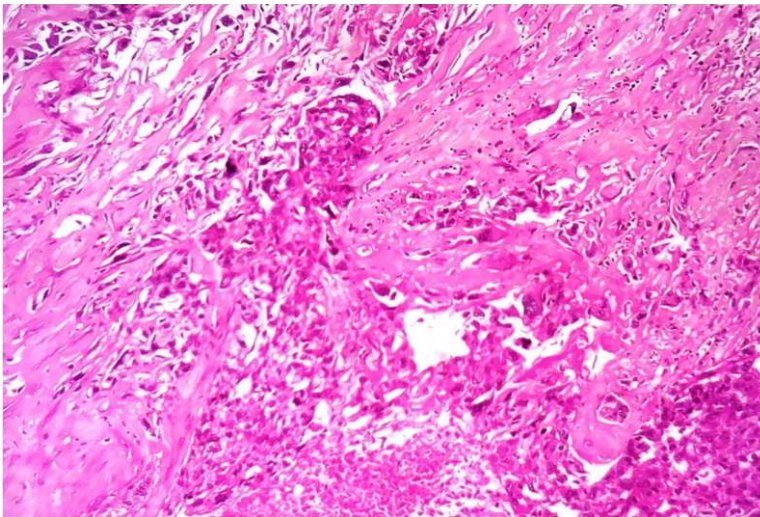
- Combination theory: It suggests that both cellular lines come from the same stem cell.
- Collision theory: It proposes that two different cellular lines with different mutations generate the tumour.
- Conversion theory: It suggests that a cellular line already carrying the mutation suffers a **metaplastic** transformation, producing a further cellular clone.

Histopathology

On gross examination, carcinosarcomas are composed of soft to firm, gray or tan solid tissues with prominent areas of hemorrhage, necrosis and cystic degeneration [19]. Occasionally, bone or cartilage may found on palpation. Histopathologically, it is composed of both carcinomatous and mesenchymal components (figure-1). Sarcomatous component can be homologous (composed of tissues **that** normally found in ovary) or heterologous

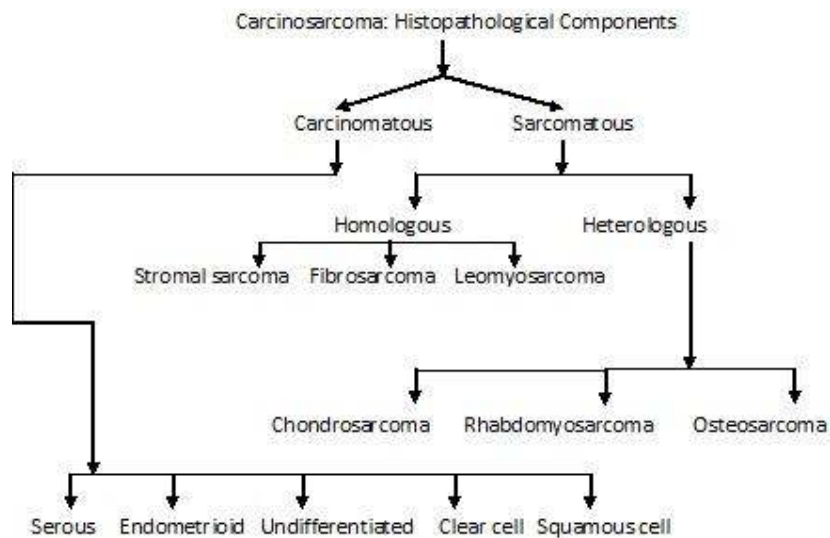
79 (composed of tissues not normally found in ovary) basing on origin of its mesenchymal
80 tissue [22]. Homogenous part may be endometrial stromal sarcoma, fibrosarcoma, and
81 leiomyosarcoma. Heterogenous part may be chondrosarcoma, rhabdomyosarcoma, and
82 osteosarcoma [23]. Carcinomatous components are usually high grade [19] and can be
83 serous, endometrioid, undifferentiated carcinoma, clear cell carcinoma or squamous cell
84 carcinoma [13,20,24]. Epithelial component mostly present in multiple forms and serous
85 components are more common than endometrioid components with an inferior prognosis
86 [25]. Clear cell and squamous cell components are rarely seen. In majority cases epithelial
87 components are responsible for tumour progression and distant metastases [26].
88 Homologous sarcomatous component do not carry a better prognosis than heterologous
89 sarcomatous components [25,27-29]. Histopathological components in carcinosarcoma of
90 ovary are described in figure-2 in schematic form.

91 Figure-1:



92
93 Figure-1 H&E 100X showing both the carcinomatous and sarcomatous components with
94 presence of necrosis in the lower field

95 Figure-2:



96

97 According to Boucher et al., equal representation of the epithelial endometrioid and serous
 98 component types in ovarian carcinosarcomas and mesenchymal component is largely
 99 heterologous, of chondromatous and rhabdomyoblastic differentiation [22]. According to
 100 Kunkel et al., **serous carcinomatous components overwhelms and also a predominance of**
 101 **heterologous chondromatous components** [30]. Menon et al found endometrioid carcinoma
 102 and heterologous rhabdomyosarcoma as predominant components [31]. According to
 103 Patnayak et al., serous carcinoma as predominant epithelial component and
 104 rhabdomyosarcoma as predominant sarcomatous component [32]. Rama K et al in a
 105 recent study showed predominant serous component with equal presentation of
 106 homologous and heterologous mesenchymal components [6].

107 Eosinophilic hyaline granules are found in carcinosarcomas and are positive on periodic
 108 acid-Schiff staining with **minority** immunoreactive for α 1-antitrypsin [19]. Singular cases
 109 have been reported with trophoblastic or neuroendocrine differentiation or alpha-
 110 fetoprotein (AFP) expression [33].

111 Histologically, immature teratoma and heterologous Sertoli-Leydig cell tumours (SLCTs)
 112 are two important differential diagnoses [19]. Immature teratoma is almost never seen in
 113 women older than 50 years age group, contains elements derived from all the three germ
 114 layers with prominent primitive neuroectodermal component, lacking malignant
 115 **mullerian-type**. Cartilage in immature teratoma has a fetal appearance, whereas cartilage
 116 in carcinosarcoma resembles poorly differentiated chondrosarcoma with marked nuclear
 117 **pleomorphism** [19]. Presence of islands of **cartilages** or rhabdomyoblasts in heterologous
 118 Sertoli-Leydig cell tumours **cause diagnosed difficult**; but presence of Leydig cells, sex cord
 119 formations, tubules or gastrointestinal-type mucinous glands or cysts facilitate the
 120 diagnosis. EMA **are** usually positive in carcinosarcomas, but occasionally seen in SLCTs.
 121 Alpha-inhibin and/or calretinin are positive in SLCTs [19].

Due to lack of standardized data on histopathological analysis, the predominant epithelial and mesenchymal components with their prognosis is still controversy and needs detail analysis at molecular level with large data for evaluation and to draw a conclusion.

Table-1: showing predominant epithelial and mesenchymal components in carcinosarcoma of ovary

Literature	Predominant Carcinomatous component	Predominant Sarcomatous component
Boucher et al (1994)	Endometrioid = serous	Heterologous (chondromatous and rhabdomyoblastic)
Kunkel et al (2012)	Serous component	Heterologous chondromatous
Menon et al (2013)	Endometrioid component	Heterologous rhabdomyosarcomatous component
Patnayak et al (2010)	Serous	Heterologous rhabdomyosarcomatous component
Rama K et al (2015)	Serous	Heterogous = homologous

Immunohistochemical examination is used for confirmation of diagnosis. It is an important tool in highlighting biphasic nature and areas of heterologous differentiation which may give a prognostic impact [6]. Cytokeratin and epithelial membrane antigen are positive for epithelial component. Vimentin, smooth muscle actin, CD10, desmin, and myoglobine are positive in mesenchymal components. S100 is used to detect chondroid or adipose tissue differentiation (figure-3) [5]. CD34 marker distinguishes ovarian carcinosarcomas from Epithelioid sarcomas, which strongly express CD34 [6]. P53 immunostatin show positivity in both carcinomatous and sarcomatous components which may suggest monoclonal theory [6].

Figure-3:

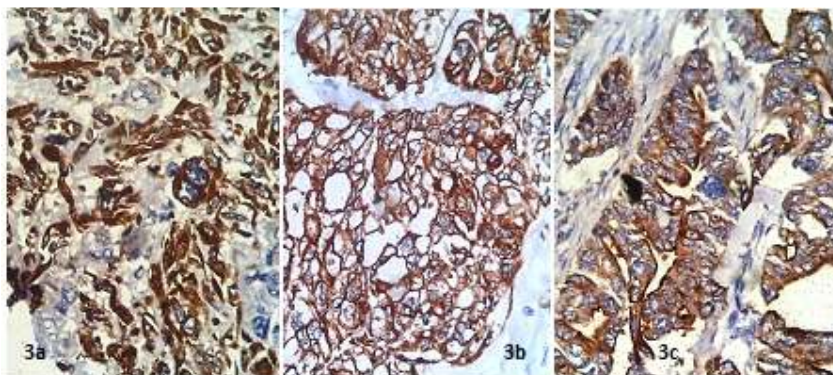


Figure-3 showing immunohistochemistry stain positive for: 3a) Vimentin in the sarcomatous component, 3b) Pan CK in the epithelial components, and 3c) EMA in the epithelial components

Clinical diagnosis

Clinical features:

Ovarian carcinosarcoma follows a distinct natural history compared to other epithelial ovarian carcinomas [5,13,16], tend to occur in older women with more often presents at disseminated disease and with inferior prognosis. Majorities have predilection for early dissemination [5,8,13,16,17]. The way of clinical presentation is similar to epithelial ovarian malignancy. Abdominal distension and pain, nausea, vomiting and weight loss are common symptomatic findings. On clinical examination, palpable mass and ascitis are common findings. Presence of epithelial and mesenchymal components behaves in independent manner particularly in metastatic patterns. Transperitoneal spread is exclusively occur by epithelial component and rarely occur by sarcomatous component [32]. Metastases usually involves serosal and peritoneal seeding. A recent study showing elevated liver parenchymal metastases in comparison to classical epithelial ovarian carcinoma; the pelvic recurrence, liver metastases and peritoneal metastases are 31%, 23% and 19% respectively [34]. Carcinosarcomas are presented with larger tumour size typically ranging from 15-20 cm in diameter [13]. A recent study showed the size of the tumours range from 8-12 cm with mean size of 10.5 cm [6].

Serum markers:

Tumour marker CA125 is elevated in 74% of patients. AFP marker is rarely elevated [35]. In a study by Menon et al., preoperative CA125 is raised in in 9 out of 12 cases of ovarian carcinosarcoma and ascetic fluid cytology analysis revealed adenocarcinomatous deposits [21]. In a case report by Patnayak et al, CA125 is elevated [31].

Imaging studies:

Ultrasonography is the initial radiological investigation of choice. Ultrasonographically tumours are large, composed of solid, cystic or mixed components with thick septa. MRI of abdomen describes the better characteristics of the tumour.

Staging classification system is similar to FIGO system applied to the other ovarian carcinosarcomas [36].

Preoperative diagnosis of the primary ovarian carcinosarcoma remains a challenging situation. Both the clinical and radiological findings are not specific for ovarian carcinosarcoma and are similar to other ovarian malignancies [37]. There is no specific

serum marker for ovarian carcinosarcoma and also cytological analysis of ascetic fluid may not give relevant components for carcinosarcoma. Data showed cytological analysis of asitic fluid in positive cases yield malignant epithelial components in majority cases [38]. The definite diagnosis of carcinosarcoma can only possible by histopathological examination of the resected specimen.

Treatment

Standard treatment consists of bilateral salpingo-oophorectomy, total abdominal hysterectomy, debulking of peritoneal metastases, and lymphadenectomy [17,18,25]. Treatment of ovarian carcinosarcoma is based upon FIGO staging. In stage I, total hysterectomy plus bilateral salpingo-oophorectomy, omentectomy, lymphadenectomy, and removal of any suspicious mass should be performed. In other stages, cytoreductive surgery should be performed like in other ovarian malignancies. The role of cytoreductive surgery is well established in epithelial ovarian carcinoma; but in carcinosarcoma it is still doubtful due to insufficient data. Recently Gynaecological oncology group (GOG) reported platinum as first line treatment with good response [36]. The role of radiation therapy is not still established [36].

Till date there is no consensus regarding optimal adjuvant chemotherapy regimens in ovarian carcinosarcoma. Many chemotherapeutic regimens already used in different centres without any standard conclusions. Women with ovarian carcinosarcoma have relatively less response to chemotherapy than epithelial ovarian cancers [17]. According to GOG, poor response rate and high toxicity with doxorubicin for ovarian carcinosarcoma. Most chemotherapeutic regimens are simplified into platinum containing regimens versus non-platinum containing regimens. Many institutions follow ifosfamide with platinum based combination regimen while others follow taxane with platinum based combination regimen. Both the ifosfamide [39] and platinum [40-42] have demonstrated efficacy in both ovarian and endometrial carcinosarcoma. Carboplatin and paclitaxel combination chemotherapy regimen has a response rate up to 72% in carcinosarcoma of the reproductive tract with more favourable toxicity profile than ifosfamide and platinum regimen [43-45]. Current idea regarding adjuvant chemotherapy is still unclear but with increase trend for favouring platinum-based therapy [46]. Literatures showed 68% overall response rate in the platinum containing regimens and 23% response rate in non-platinum containing regimens [44,47]. In an analysis of 22 patients, treatment with carboplatin and paclitaxel versus cisplatin and ifosfamide found no survival difference [48]. Rutledge and co-workers found improved survival in women with ovarian carcinosarcoma treated with ifosfamide combination regimen [49]. According to Chun et al, women who received paclitaxel/platinum-based combination chemotherapy had longer progression free interval and overall survival [10]. According to Paulsson et al, a retrospective series of 81 Swedish cases demonstrated that, compared to those with an incomplete regimen, the 57% of subjects who completed 6 cycles of platinum based chemotherapy had improved overall survival [50]. Combination chemotherapy regimen with cisplatin/ ifosfamide, and also paclitaxel/carboplatin have been tried in some studies with details [15,29,43,48,51,52,53].

A recent study shows lack of response to inhibitors of epithelial growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), insulin growth factor-1

receptor (IGF-1R), and poly ADP-ribose polymerase (PARP) indicating insufficiency of gene expression and amplification profiling to predict response [54]. Model patient heterotransplant #003 (PH003), and future ovarian carcinosarcoma tumour graft models, may be helpful to analyse for better novel therapies to improve survival outcome [54].

Prognosis

MMMT is an aggressive tumour with poor survival outcome. MMT of ovary carries more favourable prognosis than that of the uterus [18] but with worse prognosis in comparison to serous carcinoma of the ovary [17,55,56]. A case-control study with 50 women of ovarian carcinosarcoma showed 24 months of overall median survival, inferior to 41 months for women with serous carcinomas [5]. One study showed inferior survival for ovarian carcinosarcoma with advanced stage disease in comparison to that of serous carcinomas whereas no statistically significant difference in survival between these two histologic subtypes for early stage diseases [16]. In a recent study survival is inferior for all the stages of ovarian carcinosarcomas in comparison to serous carcinomas and survival was only 65% for carcinosarcomas stage I whereas 81% for those with serous carcinomas [3]. It is an aggressive subtype of epithelial cancer diagnosed at advanced stage [7,52,55,57]. The median survival is 8-16 months in MMTs [25]. In majority studies, the median survival was nearly 18 months [18,20,27,29-31,41,52]. The age and stage are associated with overall survival [7,10,17,43,58]. Age >70 years carries a significantly worse prognosis than younger patients [34]. Heterologous sarcoma component and high grade indifferntiation of the epithelial component are two poor histological prognostic factors [12]. Also, the extent of cytoreductive surgery and residual status correlate with outcome [59]. Some literature reported inferior prognosis associated with higher residual tumour burden [15,17,25,43,49,60]. According to previous data, the optimal cytoreduction means ≤2 centimeters diameter of residual disease remaining [17,43,44,57,58]. But recently the optimal cytoreduction means no longer than 1 centimeter in diameter of residual disease after primary surgery [61]. But, it is better if no gross residual disease after cytoreductive surgery [16]. In a retrospective study of ovarian carsinosarcoma by Rauh-Hain et al, patient with microscopic residual disease had OS of 47 months, those with macroscopic residual disease ≤1cm had OS of 18 months and those with suboptimal cytoreduction had OS of 8 months [5]. Patients treated with optimal cytoreduction were with medial survival of 25 months whereas it was 8 months in cases with suboptimal cytoreduction [62].

Table-2: Adverse prognostic factors

Advance age
Advance stage
Predominant epithelial tumours
Predominant serous subtype [25]
Heterologous elements [63]
Suboptimal cytoreductive surgery

Post operative higher residual disease burden
Poor response to therapy

256

257 Conclusion

258 MMT of ovary are rare tumours with aggressive behaviour, majorities present at an older
 259 age, advanced stage at the time of diagnosis and survival varies with stage of the disease
 260 and histological types. Despite all aggressive modalities of treatment there is increased risk
 261 of death with poor prognosis in comparison to epithelial ovarian carcinoma. Such rare
 262 disease with poor prognosis needs more number of prospective studies to better
 263 understand the molecular characteristics of MMT and to give idea on new therapeutic
 264 regimens to improve survival of the patients.

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