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THE OUTCOME OF PATIENTS WITH UTERINE CARCINOSARCOMA

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DECLARATION

I, **Langanani Mbodi,** hereby declare that this research is of my own work. I am submitting this research report for the fulfillment of the requirement by the MSc (Research) degree of the University of Witwatersrand.



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14th day of November 2018

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ABSTRACT

Objectives. The study aimed to determine the outcome of women with uterine carcinosarcoma and treated with surgery alone, surgery and adjuvant irradiation or surgery and adjuvant chemotherapy at Charlotte Maxeke Johannesburg Academic hospital (CMJAH).

Methods. Women with a histologically confirmed diagnosis of uterine carcinosarcoma managed with the three modalities at CMJAH were selected retrospectively over 10 years. Survival graphs were generated using the Kaplan-Meier method.

***Results*.** A total of 32 women met the inclusion criteria for the study. The mean age was 63.34 years (SD±8.65). Total Abdominal Hysterectomy (TAH) & Bilateral Salpingo-Oophorectomy (BSO) was done in 12 (37.50%), TAH/BSO/Washings in 7 (21.88%), TAH /BSO/Omentectomy in 4 (12.50%), TAH/BSO/Washings and Omentectomy in 4 (12.50%) and TAH/BSO/Lymphadenectomy (LND) & Washings in 2 (6.25%) women. There was no statistical association between survival after treatment and uterine size (p=0.638), ECOG status (p=0.571), lymphovascular invasion (p=0.687), treatment with radiotherapy (p=0.202) and recurrence period of disease. The mean survival from surgery was 15.5 months (SD± 88.79) and 11.25 months (SD±66.47) in radiotherapy group. Survival estimates calculations on chemotherapy group were difficult due to small sample.

***Conclusion*.** Treatment with radiotherapy or chemotherapy after surgery offers no survival benefit. However, this was a low powered study. The role of nuclear medicine modalities such as Targeted Alpha Therapy (TAT) in carcinosarcoma has not been well explored and perhaps it may offer better outcome.

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Abbreviations

AJCC	American Joint Committee on Cancer
aRT	Adjuvant Radiotherapy
ART	Anti-Retroviral Treatment
BSO	Bilateral Salpingo-Oophorectomy
CD4	Cluster of Differentiation 4 (T lymphocyte cell)
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
COC	Combined Oral Contraceptive
CS	Carcinosarcoma
CSS	Cause Specific Survival
DGMC	Donald Gordon Medical Center
DSS	Disease Specific Survival
DTIC	Cyclophosphamide, Vincristine, Doxorubicin, and Dacarbazine combination
DXT	Deep X-ray Therapy
ECOG	Eastern Co-operative Oncology Group
FIGO	International Federation of Obstetrics and Gynaecology
GOG	Gynecology Oncology Group
Gy	Grey (Unit of Radiation)
HIV	Human Immunodeficiency Virus
IUCD	Intrauterine Contraceptive Device
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of the Transformation Zone
LND	Lymph nodes dissection
LVI	Lympho-vascular invasion
MDT	Multi-Disciplinary Team
MMMT	Malignant Mixed Müllerian Tumor

NHLS	National Health Laboratory Services
OS	Overall Survival
ROC	Receiver Operating Characteristic
RT	Radiotherapy
SA	South Africa
SAR	Survival after Recurrence
TAH	Total Abdominal Hysterectomy
UCS	Uterine Carcinosarcoma
VL	Viral Load
WHO	World Health Organization

Definition of terminology

For the purpose of this study, the following definitions were used to describe events related surgical procedures: -

1. **Complete surgery** was defined as an instance where there was total/complete resection of all grossly visible tumour. Examples are a Total Hysterectomy, Bilateral Salpingo-Oophorectomy, Omentectomy done as indicated on pre-operative consent form.
2. **Incomplete surgery** was defined as an instance where there was either less than total removal of all tumour or the resection has been carried out in the presence of known distant metastases.
3. **Abandoned surgery** was defined as intra-operative suspension/cancellation of the planned cytoreduction operative procedure irrespective of whether a biopsy was done or not.

CHAPTER 1

Introduction

Uterine carcinosarcomas represent less than 5% of endometrial malignancies globally although there are associated with more than 15% of deaths from uterine malignancies.[1] In a 5-year retrospective reviews of endometrial cancers in Rahima Moosa Mother and Child hospital, they found that Uterine Carcinosarcoma accounted for 25.4% (14 of the 55) of the endometrial cancers. The 9-year Pretoria retrospective study on sarcomas found that 49% (24 of 49) were carcinosarcoma.[2,3] About 40% of patients present with disease outside the uterine cavity. More than 50% will recur with an overall mean survival of 21 months (84 weeks).[1]

A pilot multimodal study of 43 patients showed that combined chemotherapy and radiotherapy improves survival with a mean of 37 months (95% CI: 32 to 43 months).[1] Longer survival times were observed in the group of patients who received adjuvant Radiotherapy (aRT) compared to those who did not; as the Overall Survival (OS) was 42 months (95% CI: 37 to 52) vs. 22 months (95% CI: 19 to 25 months).[4] The overall and disease-free survivals were 31% at 1 year and 23% at 5 and 10 years on 19 women who received radiotherapy for late stage disease.[5]

Anupama R *et al*, in a six-year review of 1548 patient with gynecological malignancies of which 20 had carcinosarcoma, found that although there were no local recurrences in the six stage I and II patients treated with adjuvant radiotherapy, there was a distant recurrence. This indicated the need for a better adjuvant therapy including chemotherapy.[6]

Tumor histology (heterologous versus homologous) does not obviously impact on survival and concurrent chemoradiation appears to only improve local control with little survival advantage.[7]

Literature Review

Introduction and Background

Carcinosarcoma(CS) of the uterus, previously known as Malignant Mixed Müllerian Tumor (MMMT), is a gynecological tumor that accounts for under 5% of all uterine malignancies.[8,9,10] It is estimated that up to 16% of uterine cancer deaths may be attributed to uterine carcinosarcoma.[9] On a microscopic level, these tumors have a biphasic appearance imparted by both a malignant stromal or sarcomatous component and a malignant epithelial or carcinomatous component, which may occur in varying proportions.[1,9,10] These tumors have previously been regarded as sarcomas and staging and treatment regimens have mirrored those used for leiomyosarcomas, but of late, there has been clinical, histological and molecular confirmation of these tumors being closely associated with high-grade endometrial carcinoma.[9,10]

Predisposing factors for the development of carcinosarcoma have a similarity with those of endometrial carcinoma. This includes obesity, nulliparity, previous pelvic irradiation and exposure to tamoxifen and exogenous estrogen.[11] Four theories are postulated for the origin of carcinosarcomas:

1. Collision theory: states that two neoplastic elements had independent origins prior to their collision that resulted in a single tumor.

2. The combination theory: it suggests a bi-directional differentiation of a common stem cell precursor that resulted in carcinomatous and sarcomatous components.

3. The conversion theory advocates that the sarcomatous component is derived from the epithelial component that undergoes metaplastic differentiation.

4. The composition theory suggests that in the presence of a carcinoma, there is a pseudosarcomatous spindle cell stromal component.[11]

The current management of uterine sarcomas has an unsatisfactory outcome.[5,12] Neither adjuvant chemotherapy nor radiotherapy has improved survival for early stage uterine

sarcomas. Tumor recurrences are frequent even in cases where disease is confined to the uterus.[5] Pelvic radiotherapy has been shown to reduce the rate of pelvic relapses, and responses to chemotherapy have been demonstrated in metastatic diseases. However, survival is poor with any spread beyond the uterus.[5]

In contrast to endometrial carcinoma where extension of the radiation field beyond the pelvis may result in cure for up to 50% of females with pelvic or periaortic nodal metastases, results are disappointing with uterine carcinosarcoma[10].

Secondary carcinosarcoma may occur in women who received chemoradiation for cervical cancer. Wakayam A *et al*[13] found 0.96% of women who developed a primary second malignancy of the uterine corpus after radiotherapy (RT) at dosages ranging from 58 to 64 Gray. For a sarcoma to be considered ~~a~~ RT-associated, some criteria are proposed as follows: it should be within a previously irradiated field; a significant amount of radiation should have been given; there should be a latency period of several years (at least 3-5 years); and the tumor should be histologically proven and different from the primary neoplasm.[13]

Clinical Characteristics

Uterine Carcinosarcomas (UCS) typically present with abnormal vaginal bleeding, abdominal pain, or abdominal pain and an abdominal mass.[13,14]

Sixty percent of newly diagnosed uterine UCS patients present with advanced stage disease in which there is extension beyond the uterus.[1]

However, CS may also present in the rarest forms in other organ systems such as adrenocortical carcinosarcomas that present with epigastric pain, low grade fever, nausea/vomiting and loss of appetite.[15] Carcinosarcomas may also present within the urethra, cervix, orbit, ovary and anus.[16,17,18,19, 20,21] In addition, there may be primary peritoneal carcinosarcoma[22] and within the gallbladder[23], the presentation may be that of acute pancreatitis due to gallstones. Pulmonary carcinosarcomas may present as aspergillosis.[24]

Histopathology

This tumor's composition is from both epithelial and mesenchymal components which give rise to carcinomatous and sarcomatous components respectively.[25] The epithelial component may be of various endometrial carcinoma subtypes such as endometrioid, clear cell or serous carcinoma.[4,25] The sarcomatous component may be either homologous, in which the constituent elements may be found in the uterus such as leiomyosarcoma, or heterologous; in which the constituent components are not-found in the uterus; such as rhabdomyosarcoma [11.] Both components tend to be high grade. [4] Histopathological and molecular studies have shown origin of the sarcomatous components from the carcinomatous precursor by way of monoclonal cancer cells which give rise to the sarcomatous elements through a process of metaplastic transformation.[4,11,13] It is believed that the epithelial elements are the impetus for tumor progression. It is this evidence that advocates that the combination and conversion theories, whilst not mutually exclusive, are the predominant histogenetic pathways culminating in a biphasic tumour.[11]

It is the carcinomatous components that are responsible for invasive foci and metastatic spread of disease.[13] Recent investigations have shown that histological grade, mitotic index and presence or absence of heterologous differentiation have no impact on the overall prognosis.[11] Treatment strategies are currently evolving together with knowledge of the biological characteristics of this malignancy.[1] However, Felix *et al*.[26] state that despite previous studies suggesting that the epithelial component drives the aggressive behaviour of these tumors, there is minimal evidence to date that may predict which epithelial subtypes have worse survival.[26]

CS primarily result in lymphovascular invasion, akin to that seen in endometrial carcinomas as opposed to sarcomas which preferentially spread via the haematogenous route.[11] Most metastases and recurrences are composed of pure carcinomatous elements.[14,15]

Staging of Uterine Carcinosarcoma

The current staging system for carcinosarcoma is the same as that of endometrial carcinoma and is based on the revised International Federation of Obstetrics and Gynaecology (FIGO)

2009 guidelines. This includes lymphadenectomy (pelvic and para-aortic).[1] The aim of staging any malignancy is to predict survival and aid in deciding the best treatment strategies. Pradhan and colleagues argue that the current FIGO classification doesn't aid in reliably predicting prognosis for an aggressive tumor, that is carcinosarcoma.[27] They indicate that, based upon their reclassification of 112 patients with uterine carcinosarcoma, the revised FIGO staging system did not predict survival more accurately than former UCS staging. They strongly suggest that carcinosarcoma has an overall poor prognosis and better indicators of survival are needed.[27]

Table 1.1 Revised FIGO 2009 staging system for uterine carcinosarcomas

Stage	**Location of disease**
Stage 1	**Tumour confined to the corpus uteri**
1A	No or less than half myometrial invasion
1B	Invasion to or more than half the myometrium
Stage 2	**Tumour invades the cervical stroma but does not extend beyond uterus**
Stage 3	**Local and regional spread of the tumour**
3A	Tumour invades the serosa and/or adnexa
3B	Vaginal or parametrial involvement
3C	Metastasis to the pelvic and/or para-aortic lymph nodes
C1	Positive pelvic nodes
C2	Positive para-aortic lymph nodes with or without positive pelvic nodes
Stage 4	**Tumour invades bladder and/or bowel mucosa and/or distant metastasis**
4A	Tumour invasion of bladder and/or bowel mucosa
4B	Distant metastasis including intra-abdominal metastasis and/or inguinal lymph nodes

Prognostic Factors of Uterine Carcinosarcoma

In Cox regression analyses, the earlier the diagnosis is made within a period of 5 years of diesease, the more advanced AJCC stage at diagnosis, age ≥ 65 years, non-receipt of adjuvant radiotherapy, and African American race were each independently associated with diminished overall survival and cause-specific survival.[28]

Wu *et al*[28] examined prognostic factors in patients with leiomyosarcoma receiving chemotherapy. Their study demonstrated that older age (>50 years), advanced stage of disease (stage III or IV), large tumor size (>11 cm), and adjuvant chemotherapy had significant influence on overall survival. Stage of disease, tumor size and use of adjuvant chemotherapy are the only ones that were significant prognostic factors for recurrence-free survival by multivariate analysis.[28]

A multicenter study on leiomyosarcomas by Mayerhofer K *et al*[29] reported early tumor stage, age <50 years and absence of lymphovascular invasion as independently associated with good prognosis. The mitotic count was detected to be a strong prognostic parameter in early tumor stage but was not found to be an independent prognostic parameter in patients who had stage II–IV disease.[30] Uterine carcinosarcoma related to tamoxifen use is associated with a lower risk of deep myometrial tumor invasion (proportion of tumor with >50% invasion, 28.3% versus 48.8%, odds ratio 0.41, 95% Cl 0.23 to 0.74, p = 0.002, Fisher exact test). These women are more likely to have stage IA disease (48.4% versus 29.9%) and less likely to have stage IVB disease (7.8% versus 16.0%) compared to non-related counterparts (P= 0.034, chi-square test).[31]

Common Metastatic Regions

The metastatic disease is usually not symptomatic. The common metastatic sites include the lungs (49%), peritoneum (44%), lymph nodes (pelvic or para-aortic) (35%), adrenal gland and bone (19%), the heart or pericardium (9%), and the brain (7%). Other sites of metastasis although uncommon include the pancreas, liver, thyroid gland, eye ball and skin.[13] Pulmonary metastasis for uterine carcinosarcoma are the highest compared to other uterine malignancies.[13] Twenty (20%) percent of patients with clinical stage I or II carcinosarcomas have surgical stage III or IV disease from nodal or peritoneal spread. There is also a high rate of pelvic and abdominal metastases found in patients who have been diagnosed with a sarcoma.[5,28] In addition, the clinical, histopathologic, immunohistochemical, ultrastructural, molecular, and tissue culture data suggest that most carcinosarcomas are monoclonal metaplastic carcinomas as opposed to being a mixture of carcinoma and sarcoma. Virtually

all of the metastases have an epithelial component.[5,11] Recurrent and/ or metastatic UCS are often treated with chemotherapy.[8]

Treatment and Controversies in Management of Uterine Carcinosarcoma

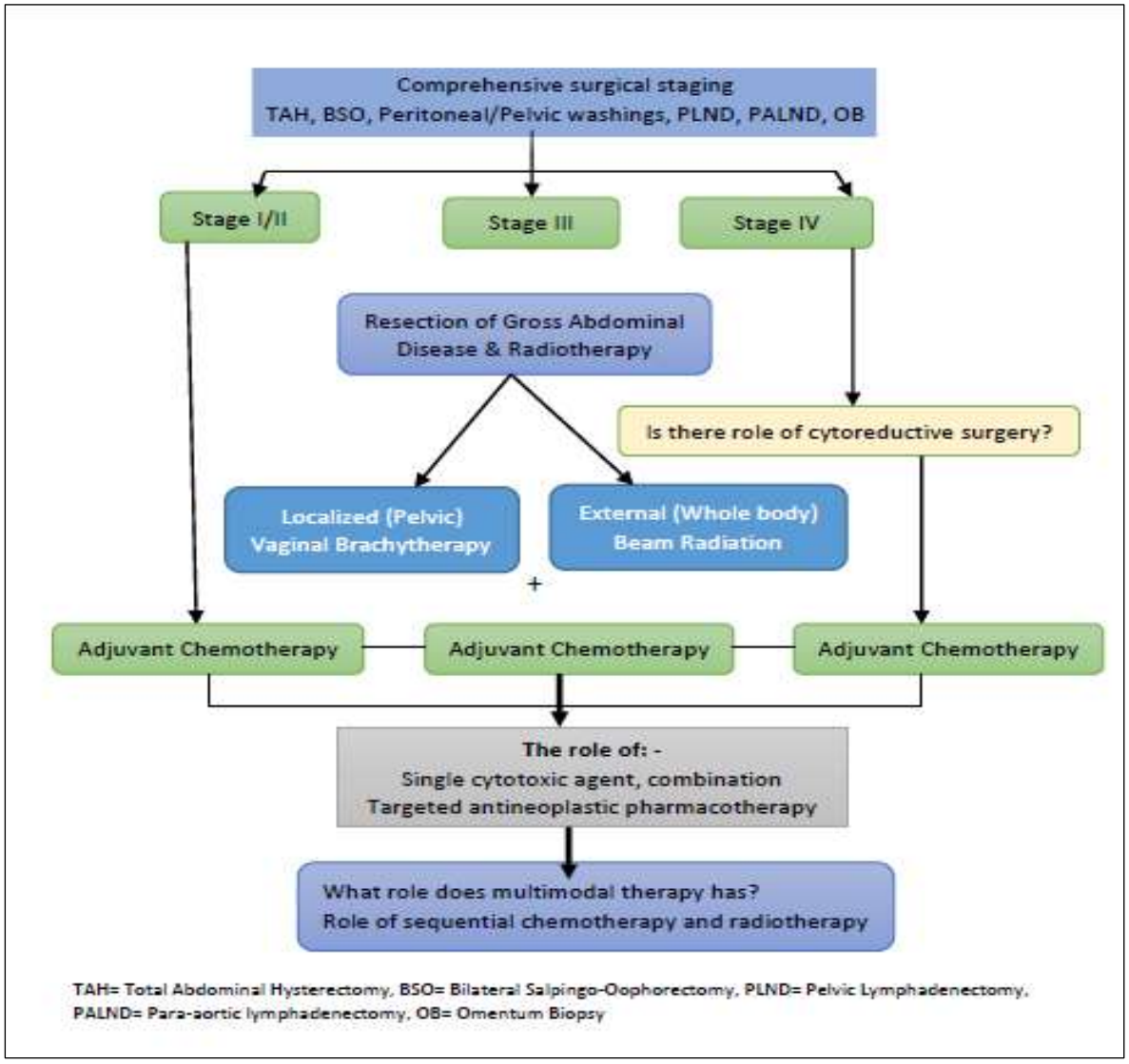


Figure 1.1 Recommendations for the treatment of uterine carcinosarcomas. (Adapted from Kanthan R *et al* [8])

Surgery

Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the standard surgical option. However, there are additional benefits from adding pelvic lymphadenectomy.

The current recommendation for a surgical approach is a total abdominal hysterectomy, lymph node dissection and peritoneal washings for staging.[8]

Arguments for lymph node dissection are that it offers control of loco-regional recurrence and improves on selecting patients for adjuvant treatment. However, lymph node dissection offers significant survival advantage for patients who are node negative.[8]

Radiotherapy

Evidence supports that radiotherapy contributes significantly to decreased pelvic recurrence. The impact of adjuvant (post-operative) therapy on patient survival is controversial and remains a subject of further research.[8] The role of radiotherapy is greater for carcinosarcomas than for leiomyosarcomas as carcinosarcomas have greater rates of pelvic and peritoneal failure following surgery.[5] Although radiation may improve loco-regional control, evidence of a true survival advantage is still uncertain. Patients with an early stage disease do not have recurrence rates exceeding 10% when treated with modern radiotherapy techniques. [8]

The techniques for radiation are still controversial. This includes the options of localized pelvic radiation by vaginal brachytherapy versus whole abdominal radiation by external beam.[13] In a retrospective study at the University of Minnesota from 1978 to 1997 [5] radiation therapy was given pre-operatively, including intracavitary brachytherapy. The treatment fields were designed primarily from operative findings and use of chemotherapy. Radiotherapy was given in daily fraction sizes of 1 Grey (Gy) to the abdomen and 1.5–1.8 Gy to the pelvic and periaortic areas. Median pelvic dose was 46 Gy (range: 40–51 Gy). Median periaortic dose was 46 Gy (range: 44–49 Gy). Vaginal surface boost doses from postoperative brachytherapy ranged from 34 to 59 Gy (median 46 Gy). A substantial fraction of women with peritoneal and nodal metastases from epithelial uterine tumors were cured with postoperative radiotherapy.[5]

Chemotherapy

There is currently no agreement on a post-operative chemotherapeutic regimen for uterine carcinosarcoma. Most of the available studies had focused on the development of post-operative adjuvant treatment for stage I/II lesions and palliative therapy for advanced stages.[8]

A pilot study [31] concluded that multimodality treatment consisting of chemotherapy with epirubicin and cisplatin as well as radiation resulted in a 74% overall survival at a median follow-up of 55 months in 38 patients with surgical stages I and II malignant mixed Müllerian tumors. However, the high dropout of participants resulted in the conclusion of multimodality treatment being controversial.

A more recent GOG study by Sutton *et al* [32] reported that 65 patients with completely resected stage I and II malignant mixed Müllerian tumors of the uterus were treated with adjuvant ifosfamide and cisplatin. The 2- and 5-year survivals were 82% and 62%, respectively. Since more than half of the recurrences involved the pelvis, the study suggested that a combined sequential approach with chemotherapy and radiotherapy may be beneficial for this group of patients, which should be verified in a randomized phase III study. Previous studies had reported that an effective adjuvant chemotherapy regimen was a combination of cyclophosphamide, vincristine, doxorubicin, and dacarbazine (DTIC)

with 68% to 89% 5-year survival in stage I uterine sarcomas.[33-37]

Women who were disease-free for ≥6months after receiving a taxane/platinum doublet had a higher 2- year Survival After Recurrence (SAR) rate compared to those who received non-taxane/platinum regimens (61.9% versus 40.0%, HR 0.46, 95% CI 0.28 to 0.75, p=0.002). In women with a disease-free interval <6months, 2-year SAR rates were similar between the two groups (20.5% versus 18.4%, HR 0.80, 95% CI 0.33 to 1.90, P=0.61).[38]

The use of Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitor agents have potential of cure in view of the angiogenesis in the gynecological carcinomas. VEGFR inhibitor Pazopanid was investigated in a phase II evaluation and the median number of two cycles was given. They found that no patients had a partial or complete response (90% confidence interval [CI]: 0%, 14.6%) with a median overall survival of 8.7 months.[39]

Outcome of Adjuvant Radiotherapy in Carcinosarcoma

Manzerova *et al* [28] found that a longer survival was observed in the group of patients who received adjuvant radiotherapy compared to those who did not. Overall survival (OS) was 42 months (95% CI: 37-52) versus 22 months respectively (95% CI: 19-25), p<0,0001. Within each stage, they observed longer survival in the irradiated patients. They also computed the 3 and 5-year rates of OS and CSS with and without adjuvant radiotherapy. The 3-and-5-year OS and CSS were greater by 5-10% for those patients who received adjuvant radiotherapy in 1999-2004 and by 15-19% in 2005-2010. Their findings suggest that further studies are warranted in the treatment of uterine carcinosarcoma, preferably in the setting of international co-operative trials.

Survival was noted to be significantly improved among patients receiving EBRT-BT combination (hazard ratio [HR] 0.72, 95% CI) but not among those receiving EBRT alone (HR 0.93, 95% CI) or BT alone (HR 0.84, 95% CI).[41]

Abdominal radiotherapy is potentially curative in patients with stage III endometrial carcinomas with peritoneal spread.[5] It has resulted in occasional long-term survival in women with stage IVB disease. In view of results of advanced endometrial carcinomas treated with radiotherapy, some studies[5] investigated the use of extended radiation field techniques with the objectives of reducing recurrences and improving survival in women with uterine sarcomas.[10] In our population, there have been no studies investigating the response, survival and reduction in recurrence in carcinosarcomas. In addition, there have not been studies examining the various morphological appearances at a microscopic level.

Survival and Recurrence of Disease

Manzerova J *et al* [4] in their review of 2342 patients from 5000 publications (data extracted from Statistics, Epidemiology and End Results (SEER) database run by the National Cancer Institute) found that there was a median follow-up time of 73 months; the median OS of 29 months (95% CI: 26–32 months) and the median cause-specific survival (CSS) of 37 months (95% CI: 32 to 43 months). After controlling for race, age and era of diagnosis, they

identified that greater survival was observed for each AJCC stage and each quinquennium of diagnosis in those patients who received adjuvant radiotherapy.

In the retrospective study of women who received radiotherapy for stages III and IV uterine sarcomas from 1978 to 1997 in Minnesota,[3] the overall survival was also poor with 31% at one year and 23% at five and ten years. Nine women had recurrence of disease and died within the first year, and one patient had tumor recurrence and died at four years. Two women died without evidence of recurrence at nine and twenty-four years respectively. However, women with leiomyosarcoma had an overall survival of 67% at one year and 33% at 5 years. Their relapse free survival was only 33% at one year and five years.

The majority of women with uterine carcinosarcoma who had tumor recurrence, had multiple initial sites of peritoneal and nodal involvement. This was not the case with leiomyosarcomas where the distant failure sites included lung, bone and brain.[5]

In the study by Rajanbabu Anupama *et al* [37], 35% of women had disease recurrence and one patient with advanced disease in whom complete tumor debulking could not be achieved, had progressive disease. Two patients had tumor recurrence in the vaginal vault and the remaining five had distant recurrences. Both vaginal vault recurrence patients had stage I disease but node dissection was not performed as part of staging and they had not received adjuvant therapy.

The findings by Seagle[40] on stage 1 carcinosarcoma of 5614 women over 15 years supports the idea that a Hysterectomy with lymphadenectomy to at least 15-20 removed nodes is associated with increased survival of women with node-negative uterine carcinosarcoma. Adjuvant treatment with vaginal brachytherapy and multiagent chemotherapy was associated with increased survival in their study.[40]

Poor survival in carcinosarcomas cases remained statistically significant after adjustment for FIGO stage. In a case-control study [26] of 45 carcinosarcomas cases and 45 high-grade endometrioid, clear cell, and serous carcinomas, the median overall survival (OS) was twice as long in the heterogeneous endometrial cancer group compared to carcinosarcomas.

Survival per stages of carcinosarcoma is as described below from Arend R et al.[1]

Table 1.2 5-year survival of uterine carcinosarcoma according to main disease stages

Stage	5-year survival	Range
IA	62%	57–68%
IB	55%	52–59%
IC	39%	33–44%
II	33%	29–38%
III	24%	21–27%
IV	9%	7–11%

Problem Statement

Despite the advances in adjuvant therapy for carcinosarcoma, the past four decades have not witnessed any measurable improvement in survival worldwide and in our setting. Based on the poor survival, it is suggested that the primary curative treatment is surgical resection. A multimodality treatment plan that includes radiotherapy, chemotherapy and a combination therapy has been suggested with some research findings indicating that surgery followed by a combination of both chemotherapy and radiation therapy offers a significantly improved outcome in the form of longer median disease-specific survival (DSS) of 31 months compared with surgery alone (DSS = 3 months), radiation therapy alone (DSS = 15 months), or chemotherapy alone (DSS = 14 months).)[8]

Justification for the study

The outcome of patients with carcinosarcoma has been reported as poor globally. The optimal adjuvant treatment for this disease is yet to be established, highlighting the need for larger multicentered studies on Carcinosarcoma. [7] In our setting, carcinosarcoma patients are treated with surgical resection, neo-adjuvant & adjuvant radiotherapy or chemotherapy. However, in the past 10-15 years, lymphadenectomy was not routinely done even through it is a recommended by FIGO. Patients receive radiotherapy (brachytherapy and pelvic radiation) to reduce local recurrence and pelvic recurrence as well as chemotherapy to treat systemic/advanced disease. The extent of the problem is not documented and it is not known whether any treatment modality offer better survival outcome over the other.

CHAPTER 2

Aim of the Study

Our research aims to examine the outcome of patients who were treated with surgery, radiotherapy, chemotherapy and those who received adjuvant treatment in all surgical stages of carcinosarcoma at Charlotte Maxeke Johannesburg Academic Hospital. The study also aims to compare the various histological appearances of these tumors in contrast to current literature.

Objectives of the Study

1. To describe clinical characteristics and demographics of patients treated for carcinosarcoma.
2. To describe the stages at which women with carcinosarcoma at Charlotte Maxeke Johannesburg Academic hospital present.
3. To describe overall survival and disease-free survival of patients treated for carcinosarcoma.
4. Compare the outcome of women treated with surgery alone, radiotherapy alone, surgery & radiotherapy, and surgery & chemotherapy.
5. To determine common complications related to the treatment (chemotherapy, radiotherapy, surgery or combination therapy).

Research Methods

Study Setting

Women who had a confirmed diagnosis of uterine carcinosarcoma managed with radiotherapy, chemotherapy or surgery alone at Charlotte Maxeke Johannesburg Academic Hospital (at both the Gynecological oncology and Radiotherapy units) and were above 18 years of age.

Study Sample

All women who had carcinosarcoma diagnosed on histology, whether from a pre-operative biopsy or post-operative specimen. The study was a retrospective for the period of 10 years (January 2007 to December 2016) of patients treated at Charlotte Maxeke Johannesburg Academic Hospital Radiation Oncology department.

Sample Size

Sample size estimation was based on the key research question to be answered, in this case, comparing the major two groups (surgery alone and surgery and radiotherapy) and their outcome at follow-up between the treatment groups. This required the use of a chi-square test, typically for a 4x2 table (for 4 treatment groups and binary outcomes). For the detection of a small, medium, and large effect size (w=0.1, 0.3, 0.5 respectively), sample sizes of 1091, 122 and 44, respectively, were required. We typically aimed for the detection of at least a medium effect size, should it exist. Thus, a minimum sample size of 122 was recommended. We had estimated that the sample size over the 10-year study period should be in the region of 180-200. However, only 32 women met the inclusion criteria. This we presume is due to the fact that this disease is rare.

Study Design

This was a retrospective record review.

Data collection

Data was collected from patients' records using a data collection sheet (Annexure 1). All data was retrospective for a period of 10 years and no patients were interviewed either directly or through a questionnaire. The report on histology and immunohistochemistry was retrieved from the National Health Laboratory Services electronic records. Where available, the histological tissue sections (slides) were reassessed by the pathologist and the initial diagnosis confirmed. Demographic data, presentation, risk factors and other clinical information were retrieved from hospital records after patients were identified as having been diagnosed with carcinosarcoma for which they were surgically managed, received chemotherapy, received radiotherapy or presented at the MDT meeting.

Data Analysis

Categorical variables were summarised by frequency and percentage tabulation, and also illustrated by means of bar charts. Continuous variables were summarised by the mean, standard deviation, median and interquartile range and their distribution illustrated by means of histograms. Survival data for a period of study was presented by the Kaplan-Meier survival curves and survival estimates.

The Chi squared test was used to assess the relationships between groups, demographic and clinical characteristics, staging, morphological appearance of carcinosarcoma.

Fisher's exact test was used where the requirements for the Chi squared test cannot be met. Cox proportional hazards regression were used to analyse the relationship between treatment group and survival as well as disease recurrence.

Data analysis was carried out in STATA and the 5% significance level was used. Data was collected through the data collection tool and was transferred into STATA program for analysis.

Tools Used

A data collection sheet was used to collect data from patients' records/files and post-operative histology onto an Excel document and other results were retrieved from the National Health Laboratory Services (NHLS) LabTrack system. A computer with internet access was used to capture data.

Ethical Issues

Permission to use data from the Radiation Oncology department was granted by the head of the department. Permission was also granted by the office of the Chief Executive Officer of the Charlotte Maxeke Johannesburg Academic Hospital (See Annexure 2 & 3 respectively). In addition, permission was also granted by the Department of Anatomical Pathology for use of archived histology tissue sections and reports (See Annexure 4). The study was conducted after approval and permission from Wits Human Ethics committee (HREC number M170944) (See Annexure 5). No patient identifiers were used or stored in any form and each patient was assigned a study number.

CHAPTER 3: Results

Study Population and Exclusions

A total of 40 women who had carcinosarcoma were identified from the admission book at the Charlotte Maxeke Johannesburg Academic Hospital Gynaecological Oncology Unit for the presiding 10 years. The admission diagnosis was based on histology from the tissue sample and some based on clinical assessment. Only 32 women had biopsy proven diagnosis of carcinosarcoma and were the final cases included on the list. The inclusion and exclusion criteria are as listed below in figure 3.1.

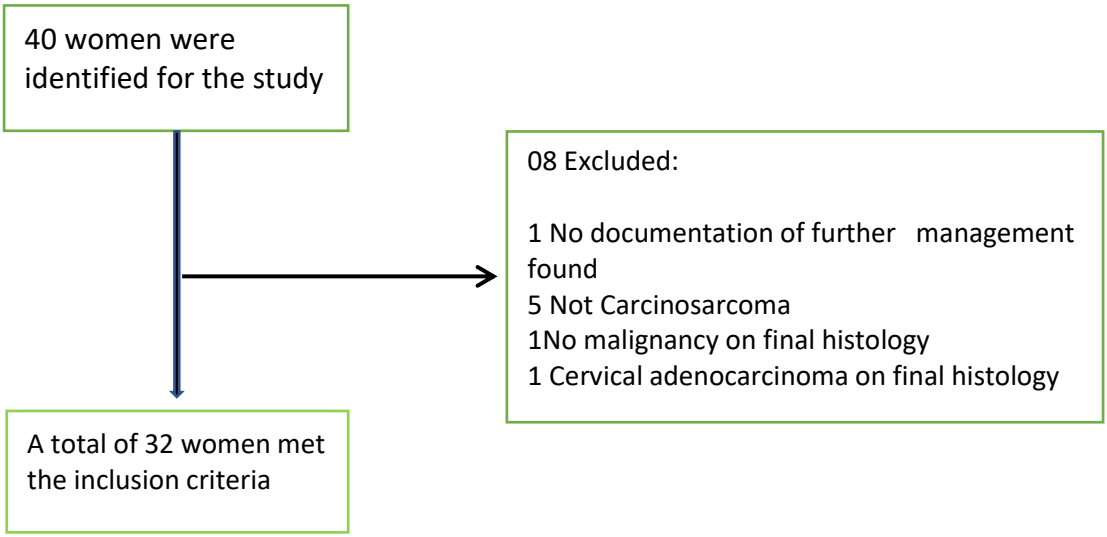


Figure 3.1 Eligibility and inclusion criteria

Demographics

The mean age of our population was 63.34 years (SD±8.65) with range 44 to 81 years. The mean parity was 3.16(SD±2.6) with a range of 0 to 8.

There were 27 (84.38%) who were of African race, 3 (9.38%) who were white and 1 (3.13% patient was coloured/mixed race. There was no record of racial grouping on 1(3.13%). There

were 19 (59.38%) women who were pensioners (old-aged), 7 (21.88%) who were unemployed and 6 (18.75%) women who were employed.

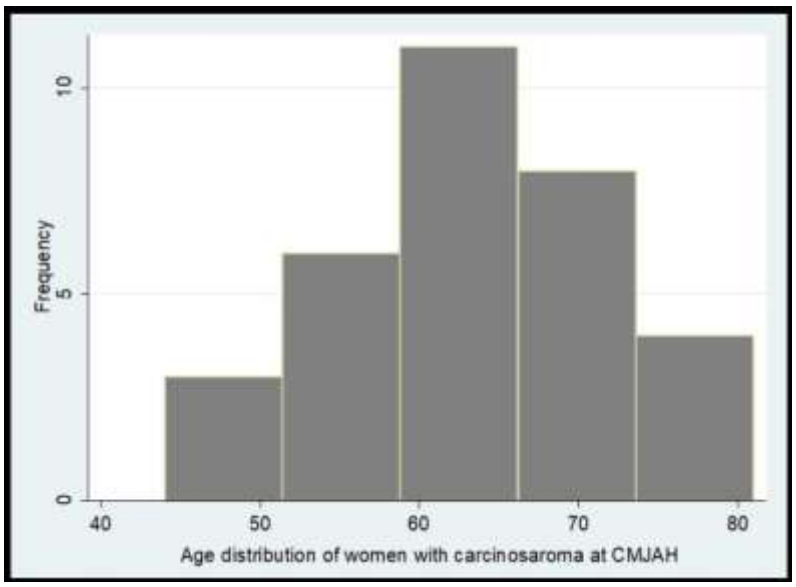


Figure 3.2: The age distribution of women with carcinosarcoma

The women who had been on hormonal contraceptives used them for a mean period of 1.4 years. The mean weight for these women was 85.23kg (SD±17.93) with mean BMI of 36.96kg/m^2 (range 24.86-61.29). There were 7 (21.88%) women who were unemployed and 19 (59.38%) who were old age pensioners receiving a state grant. There were 6(18.75%) patients who were employed.

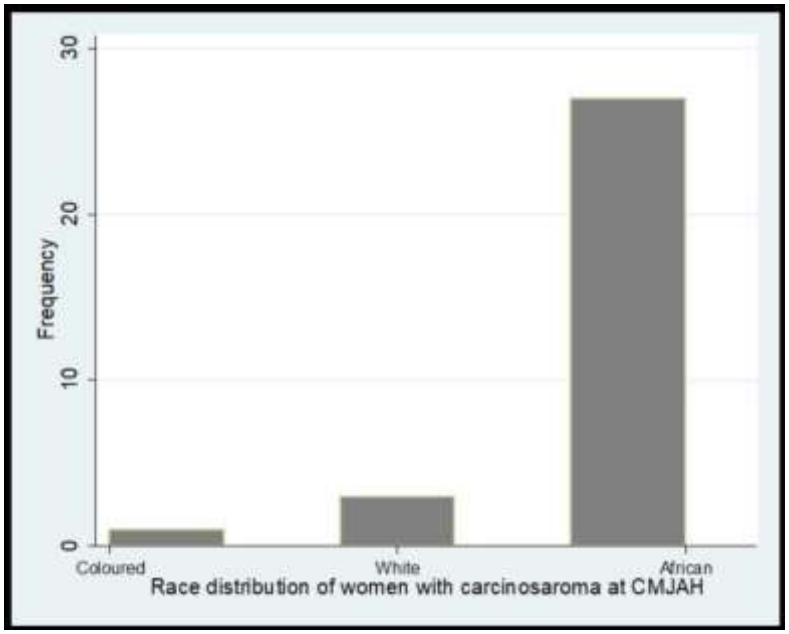


Figure 3.3: The distribution of women with carcinosarcoma by race at CMJAH

The mean post-menopausal period was 11.85 years (SD±7.19) with a range from 2 to 26 years.

Risk factors

The mean albumin level was 31.52g/l (SD±8.94) with range from lowest 11 to 45g/l. The hemoglobin level at admission was a 10.46g/dl (SD±2.11) with ranges from 6.3g/dl to 14.6g/dl.

The renal function assessment on admission showed that women had renal dysfunction with a mean creatinine of 94.63 mmol/l (SD±55.58) with ranges from 43mmol/l to 310mmol/l.

The majority of these carcinosarcoma were diagnosis at first tissue sampling/collection. The number of times the endometrial specimen was collected before the diagnosis was made was on average, 1.18 times (SD±0.59).

The use of contraceptives was unknown in 13 (39.39%) women. There were 8 (24.24%) women who used combined oral contraceptives before, 2 (6.06%) who previously used IUCDs, and 9 (27.27%) patients who never used contraceptives. Ten women had a known history of contraceptives use. The period of contraceptives use was unknown in 3 (30%) of

those who used contraceptives. Two (2) (20%) used contraceptives for a period less than 5 year. There were 3 (30%) who used contraceptives for period 5-10 years. Two (2) women used contraceptive for more than 10 years.

HIV status was known in 31 (96.88%) women. There were 3 (9.38%) patients who were HIV positive and 28 (87.50%) who were HIV negative. There was only 1 woman for whom a CD4 count was found or recorded as 214 copies/ml.

There were 31 of 32 women for whom chronic disease status was known. There were 26 (83.83%) who were Hypertensive and 9 (29.03%) diagnosed with Diabetes Mellitus. There were 4 women who had both Diabetes Mellitus and Hypertension.

The majority of women in our study had never used HRT. The history of HRT use was unknown in 2(6.45%) women. There were 2(6.45%) women who had used HRT before and 27 (87.10%) women had never used HRT.

The history of Tamoxifen use was unknown in 2(6.45%) women. There was 1(3.23%) woman who used Tamoxifen before and there were 28 (90.32%) women who had never used Tamoxifen.

There were 5(16.13%) women in whom a history of cigarette smoking was unknown. There were 2 (6.45%) women who were still smoking at the period of admission, procedure and treatment. Twenty-two (22) (70.93%) women had never smoked cigarettes, and 2(6.45%) women previously smoked cigarettes.

There were 6 (19.35%) women who had a family history of malignancy, 18(58.06%) who had no family history of malignancy and a family history was unknown in 7 (22.58%) women.

Of the six women who had a positive family history of malignancy, 3(50%) patients had breast carcinoma in their family, breast, 1(16.67%) patient had a family member afflicted by both colonic and oesophageal carcinoma and in 2(33.33%) women the type of malignancy in family members were unknown. There was missing data on most of the patients regarding their level of education. However, there was 1 (3.13%) woman who had tertiary education and 1 (3.13%) who had a matric certificate. The remainder of the study population, 30 (93.75%) did not have data available regarding their level of education.

Clinico-pathological factors

Abdominal distension was the commonest presenting problem (n=9, 28.13%), followed by Abdominal pain (n=8, 25.00%) and vaginal discharge (n=8, 25%). There were 2 (6.25%) patients who presented with abnormal per vaginal bleeding. The first presenting problem was unknown in 5(15.63%) women.

There was a pre-operative diagnostic histology of carcinosarcoma in 27(84.38%) women. A histological diagnosis of a being polyp was noted in 1(3.13%) woman. Other histological diagnoses included: other malignancies in 2(6.25%) women, an inconclusive report in 1(3.13%) woman and no histology 1(3.13%) patient who was operated based on her clinical presentation of post-menopausal bleeding.

The commonest method for specimen collection was a punch biopsy (n=14, 43.75%) of the mass. Specimen collection was via an endo-sample in 12(37.50%), DD&C in 2(6,25%), 2(6.25%) hysteroscopic directed biopsy in 2(6.25%) and 1(3.13%) patient underwent a polypectomy. It was unknown how the specimen was collected in 1(3.13%) patient.

The histology report was available in less than 6 weeks from time of collection in 28(87.50%) women, in 6 to 8 weeks in 3(9.38%) and there was no histology for 1(3.93%) patient in the file and the old deactivated “DISA” system could not be accessed. There were no histology results that were delayed and obtained after 8, 10 or 12 weeks.

The specimen was only collected once in 26(81.25%) of women. The specimen collection had to be repeated before a histological diagnosis was made in 3(9.38%) of women and undertaken 3 or more times in 2(6.25%) women. The number of times the specimen was collected was unknown in 1(3.13%) woman as this patient was clinically diagnosed.

The histology at first specimen collection (pre-operative) was reported as carcinosarcoma in 26(81.25%) women, adenocarcinoma in 1(3.13%), adenosarcoma in 1(3.13%), chronic endometritis in 1(3.13%), polyp in 1(3.13%) and suspicious of carcinosarcoma in 1 (3.13%). Pre-operative histological diagnosis was not known in 1(3.13%) woman who was operated based on clinical suspicion of endometrial cancer when she presented with post-menopausal bleeding.

The majority of women had a uterus/uterine mass of average size on admission. The uterus was assessed to be equivalent to a 6-12-week gravid uterus in 2(6.25%), 13-20-week size gravid uterus in 16(50%) women, and more than 20 weeks size in 7(21.88%) patients. There was no record of estimated uterine size pre-operatively in 7(21.88%) women. This could translate to that surgery is expected to be reasonably not difficult and likely to be completed. The uterus was assessed as mobile on clinical examination in 18(56.25%) women and fixed in 8(25.00%) patients. There were no records of the mobility of the uterus in 6 (18.75%) women.

The chronic medical condition investigated and identified on records were hypertension and diabetes mellitus. These two conditions are also commonly associated with uterine malignancy. Chronic medical conditions were reasonably controlled/stabilized in 20(62.50%) women and uncontrolled in 7(21.88%) of those who had records of such diseases. The state of medical condition control was unknown in 2 (6.25%) women. Three women did not have any chronic medical conditions pre-operative or pretherapy.

The Eastern Cooperative Oncology Group (ECOG) functional score in the cohort was ECOG 1 in 12(37.50%)) and ECOG 2 in12(37.50%). ECOG 3 or more was recorded in 4(12.50%) women. The functional status was unknown or not recorded and could not be deduced in 4(12.50%) women.

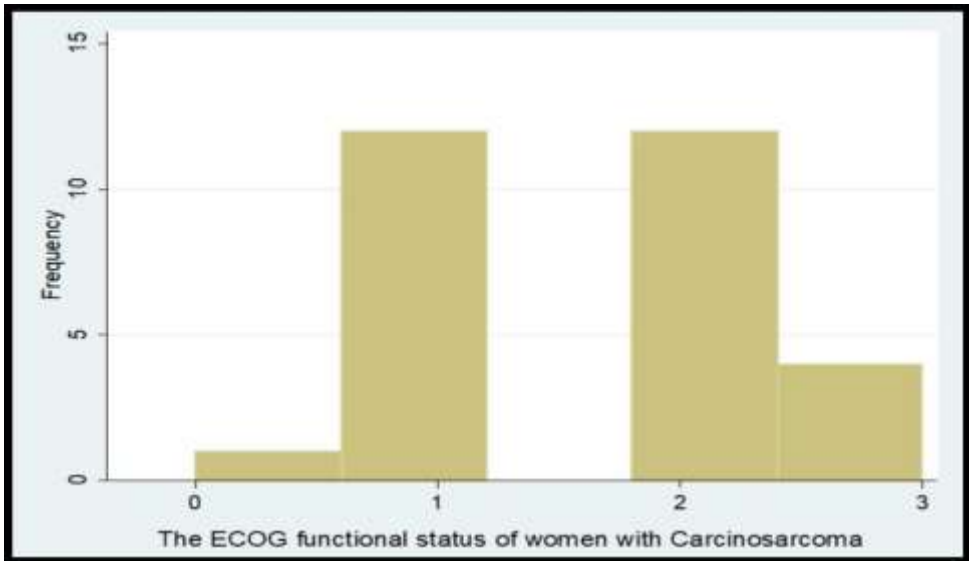


Figure 3.4: The Functional status of women admitted for surgery for carcinosarcoma

Ultrasound assessment and confirmation of ascites was made in 2 (6.25%) women, hydronephrosis was diagnosed in 6 (18.75%) patients, evidence of distant metastasis was found in 1 (3.13%) woman, both ascites and hydronephrosis was noted in 1 (3.13%) patient and ultrasound findings were unknown in 1 (3.13%) woman. There were normal ultrasound findings in 21 (65.63%) women on ultrasound examination. Chest radiography assessment was reported as normal in 29 (90.63%) women. There were 2 (6.25%) patients in whom it was unknown if chest radiography was done and what the findings were. One woman, (3.13%) had solid metastases on chest x-ray. The Clinicopathologic characteristics of the cohort of patients with carcinosarcoma were as described below.

Table 3.1. The Clinicopathologic characteristics of the cohort of patients with carcinosarcoma

Characteristics	**Number**	**%**
Age at surgery		
<60 years	12	37.50
>60 year	20	62.50
Surgery		
TAH with BSO	12	37.50
TAH with BSO + Washings	7	21.88
TAH with BSO + LND+ Washings	2	6.25
TAH with BSO + Omentectomy	4	12.50
TAH with BSO + Washings + Omentectomy	4	12.50
No surgery done	3	9.38
Stage at presentation		
Stage 1	12	37.50
Stage 2	6	18.75
Stage 3	7	21,88
Stage 4	6	18.75
Unknown	1	3.13
Tumor differentiation	N= 5	
rhabdoid	9	60.00
rhabdoid & chondroid	2	13.33
rhabdoid & osteoid	2	13.33
osteoid & chondroid	1	6.67
osteoid	1	6.67
LVI		
positive	10	31.25
negative	14	43.75
unknown	8	25.00

Surgery and surgical outcomes

The majority of women who were treated with surgery were operated on with no significant delay from the time of histopathological diagnosis. Of the women that were operated on, surgery was done in less than 6 weeks from the period of diagnosis in 9 (31.03%) women, 6-8 weeks in 8 (27.59%) patients, 9-12 weeks in 7 (24.14%) women and more than 12 weeks in 4 (13.79%) women. The reason for the delay in surgery was unknown in 1 (3.45%) woman.

The commonest surgery done for carcinosarcoma was a combination of TAH & BSO (n=12, 37.50%). Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy and Lymphadenectomy & Washings was done in 2 (6.25%) women. There was no surgery done in 3 (9.38%) women. The complete statistics of the type of surgery are tabulated in table 3.1 above.

The majority of women had an early pathological stage of carcinosarcoma. The histopathological-surgical stage of disease was 1A in 8 (25%), 1B in 4 (12.50%). There were 37.50% of patients who had stage 1 disease. There were 6 (18.75%) who had stage 2 tumors. The late stages of disease were as per table 3.1 above. However, there were 2(6.25%) patients who had stage 3A disease, 3 (9.38%) who had stage 3B tumors and 2 (6.25%) who had stage 3C disease. There was 1 (3.13%) patient who did not have histopathological-surgical staging because surgery was not done.

The common surgical complications were sepsis/infection in (n=3, 10.34%) and wound sepsis/dehiscence (n=3, 10.34%). There was 1 (3.45%) patient who had visceral injury (bladder), 1 (3.45%) who had a repeat laparotomy, 1 (3.45%) who had post-operative Deep Venous Thrombosis (DVT), 1 (3.45%) who had ileus, and 1 (3.45%) who had both intraoperative hemorrhage and visceral injury. There were no complications observed in 18 (62.07%) women.

Surgery was completed in 23 (79.31%) patients, incomplete in 4 (13.79%) women and abandoned in 2 (6.90%) women.

The findings on peritoneal washings are skewed due to change in guidelines and surgeon's practices over time. Peritoneal washings were positive in 5 (15.63%) and negative in 5

women (15.63%). There were no peritoneal washings done in 19 (59.38%) women. There were no available cytology reports on 3 (9.38%) patients in whom peritoneal washings were done.

Heterologous differentiation was confirmed in 15 women; of which rhabdoid differentiation was the commonest. There were 9(60.00%) patients who had rhabdoid differentiation, 2 (13.33%) patients had both rhabdoid and osteoid differentiation, 1 (6.67%) woman had rhabdoid and chondroid differentiation, 1 (6.67%) patient had osteoid and chondroid differentiation, 1 (6.67%) woman had chondroid and rhabdoid differentiation and 1 patient (6.67%) had osteoid differentiation.

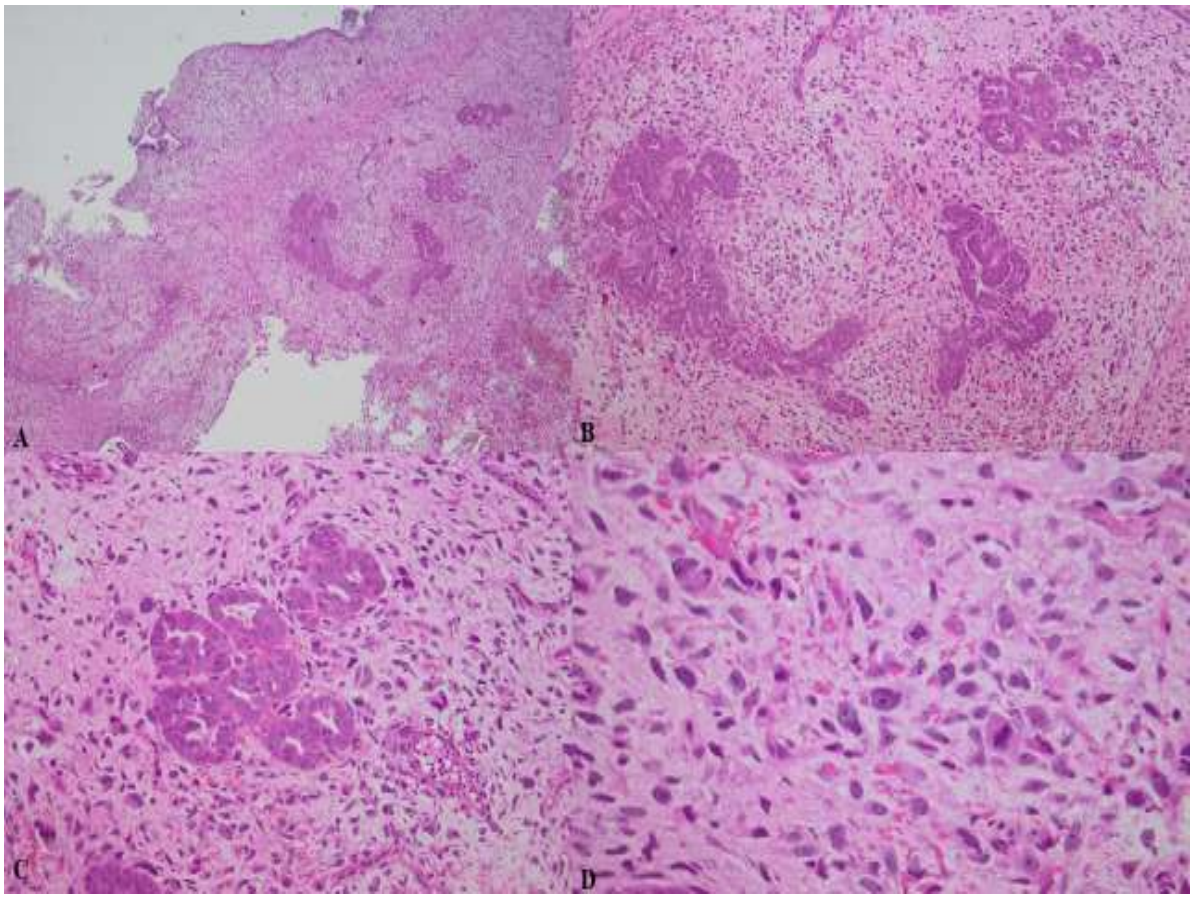


Figure 3.5. A carcinosarcoma is shown in photomicrographs A to D. A and B demonstrate both carcinomatous and mesenchymal component. C shows the malignant epithelial component whilst D illustrates the malignant stroma. H&E, 2µm sections; Original magnifications 100x (A), 200x (B), 200x (C) and 400x(D).

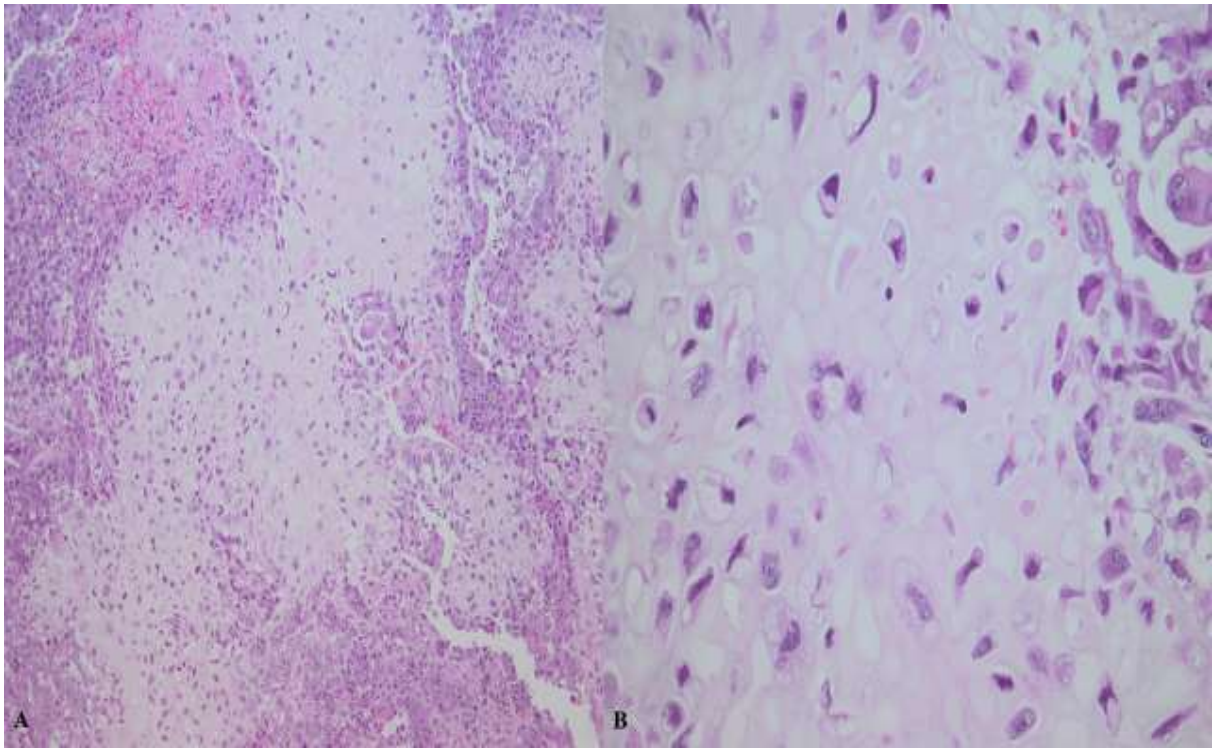


Figure 3.6. This photomicrograph demonstrates cartilaginous differentiation in a carcinosarcoma. H&E, 2µm sections; Original magnifications 200x (A), 400x (B).

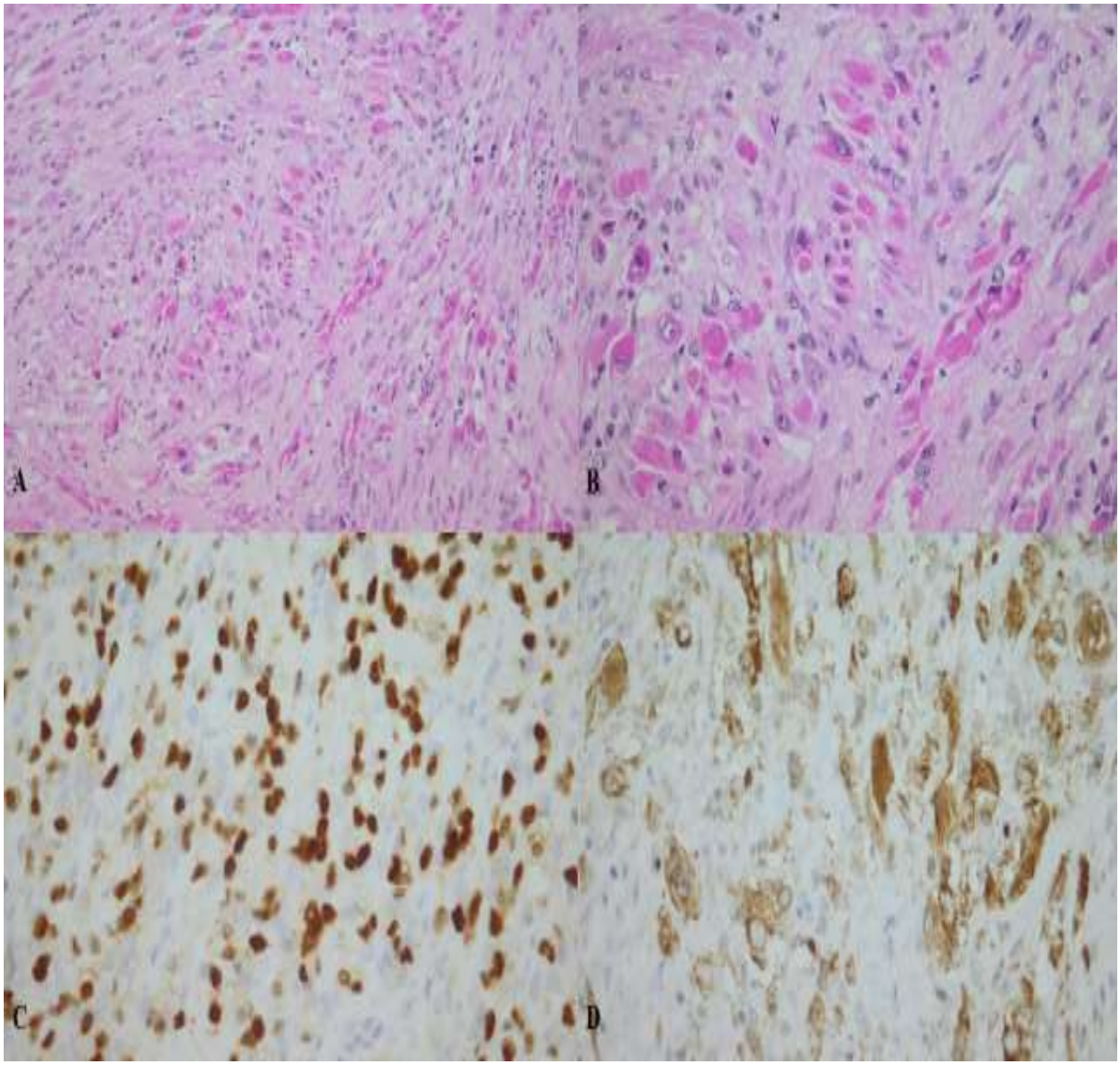


Figure 3.7. This photomicrograph shows rhabdomyoblastic differentiation in a carcinosarcoma. A and B demonstrate brightly eosinophilic rhabdomyoblastic cells in the stroma. C shows the nuclear staining with a MyoD1 stain whilst D illustrates nuclear staining on a Myogenin stain. H&E, 2µm sections; 4µm Immunohistochemical stains. Original magnifications 200x (A), 400x (B), 400x (C) and 400x(D).

There was lymphovascular invasion in 10 (31.25%) women and no vascular invasion in 14 (43.75%). Lympho-vascular involvement was unknown/not reported in 8 (25.00%) women.

Immunohistochemical stains demonstrated positive staining for AE1/3, MNF116, EMA. In addition, in cases Desmin positivity was seen together with nuclear positivity for both Myo-

D1 and Myogenin in cases where rhabdomyoblastic differentiation was noted on routine H&E staining.

Post-operative hospitalization was 3 days in 12 (37.50%) patients, 4-7 days in 7 (21.88%) women, 8-14 days in 5 (15.63%) patients, and 14 days and more in 2 (6.25%) women. -The duration of hospital stay was unknown in 6(18.75%) of patients.

Radiotherapy and Chemotherapy

Radiotherapy was given as both primary therapy and adjuvant treatment with chemotherapy to sensitive tumor response to ionizing radiation. Chemotherapy was also given as stand-alone treatment in two women with distant metastasis (Stage 4 disease).

Table 3.2: Radiotherapy for Carcinosarcoma in the past 10 years at CMJAH Radiation Oncology

	N	**%**	**Cumulative%**
Unknown	4	12.50	12.50
Given	15	46.88	59.38
Not Given	13	40.63	100.00
Total	**32**	**100.00**	
Primary therapy	2	13.33	13.33
Adjuvant	13	86.67	100.00
Total	**15**	**100.00**	

A full cycle of radiation was given to 14 women and 1 woman who was not operable received a once-off 8 Gy dose of ionizing radiation. It is unclear why the other women were not offered radiotherapy except the two women who received chemotherapy due to stage 4 disease. The mean radiation dose given for women who underwent radiotherapy was 39.93 Gy (SD±10.03) with the smallest dose given of 7 Gy and the largest; 48 Gy at mean fractions of 17.5 (SD±5.15). The smallest fractionation was 3 and the biggest fractionation was 24.

The mean brachytherapy dose given to the vault was 9.90 Gy (SD±4.98) (range 5-18) given at mean fractions of 2.72 Gy (SD±1.00) with a range of 1 to 5 fractions.

A mean dose of 9.33 Gy (1.15) was given as a pelvic boost radiotherapy for 2 women who had local recurrence and 1 woman who was inoperable.

Of the 15 women who were treated with radiotherapy, the majority (n=14, 93.33%) were compliant to the radiotherapy program and completed their treatment as planned. One woman (6.67%) defaulted the program but presented again at later stage.

Complications were recorded in 9 (60%) of the 15 women who received radiotherapy. The range of complications is listed in the table below. The complications were widely distributed.

Table 3.3: Complications observed on 9 of the 15 women who were treated with radiotherapy.

Complication(s)	**Number**	**Percentage (%)**
Desquamation	4	33.33
Diarrhoea	3	25.00
Urinary incontinence	2	16.66
Epistaxis	1	8.33
Vesico-Vaginal Fistula	1	8.33
Vaginal stenosis	1	8.33

There were 2 women who received a full cycle of chemotherapeutic agents only due to advanced disease (Stage 4a and 4b) before surgery. The regimens used were a combination of Adriamycin, Cyclophosphamide and Rituximab and a combination of Adriamycin and Isofsomide.

Survival and Follow up

There were 4 (30.77%) women who survived beyond 12 months after therapy, 3 (23.08%) who survived between 6 and12 months, 1 (7.69%) survived between 3 and 6 months and 3 (23.08%) survived for less than 3 months after therapy. The survival period was unknown in 2 (15.38%) women.

Recurrence after surgery was known in 15 women. There was recurrence within 6 months from surgery in 1 (5.56%) woman, in period 6 to 12 months in 5 (27.78%) women, 3 (16.67%) women had recurrence after 12 months and 6 (33.33%) women had no recurrence. The recurrence period was unknown in 6 (16.67%) women.

The site of recurrence was the vault in 4 (36.36%) women. One (1) (9.09%) patient had recurrence at both distant sites and vault. There was abdominal recurrence in 2 (18.18%) women. There were distant metastases in 3 (27.27%) women.

There were 18 (56.25%) who were confirmed dead, 5 (15.63%) who were still alive and it was not known if 9 (28.13%) were alive or dead at the period of the study. The cause of death was unknown in 4 women (22.22%). There were 11 women (66.67%) who died from dissemination of the disease/malignancy, 1 (5.56%) woman died from complications of wound sepsis and 1 (5.56%) patient died from both complications of her medical condition and dissemination of the malignancy.

The mean survival period from date of surgery to death / last clinical visit was 15.5 months (62 weeks) (SD± 88.79). The mean survival period from date of radiotherapy to death/last seen was 11.25 months (45.87 weeks) (SD±66.47).

The women who never smoked cigarettes had 20% (Pearson $Chi^2(8) = 18.20$, $p=0.02$) chance of surviving for more than 12 months after treatment (surgery and/or radiotherapy).

Women with history of previous smoking had 10% (Pearson $Chi^2(8) = 18.20$, $p=0.02$) likelihood of surviving for only 3-6 months after treatment.

Women of African race were 4 times (Pearson $Chi^2(8) = 26.00$, $p=0.001$) more likely to survive for more than 12 months after treatment (surgery and/or radiotherapy) than both white and coloured women. They were also 3 times (Pearson $Chi^2(8) = 26.00$, $p=0.001$) more likely to survive for 6-12 months after treatment than the other two groups.

There was no statistical association between survival after treatment and uterine size at admission ($p=0.638$), ECOG status ($p=0.571$), LVI ($p=0.687$), treatment with radiotherapy ($p=0.202$) and recurrence period of disease. ($p=0.086$).

The Kaplan-Meier survivor graphs below shows survival on both the women who had surgery alone and those who received radiotherapy after surgery.

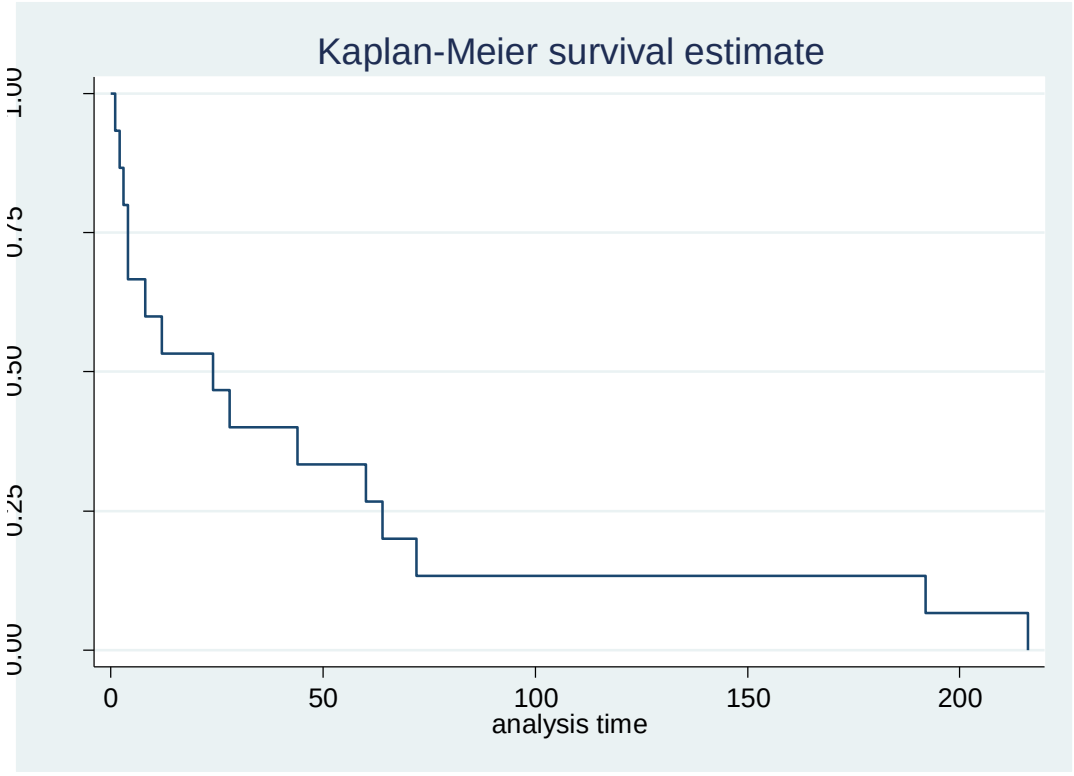


Figure 3.8: Kaplan Meier survival estimates of thirteen (13) women who were treated with adjuvant radiotherapy. (Calculated from last treatment until last time seen. The survival period is in weeks).

The survival of women at or around 60 weeks (15 months) after radiotherapy was 25%. At period more than 60 weeks, the chance of survival drastically dropped to 12.5% and continued to be this low.

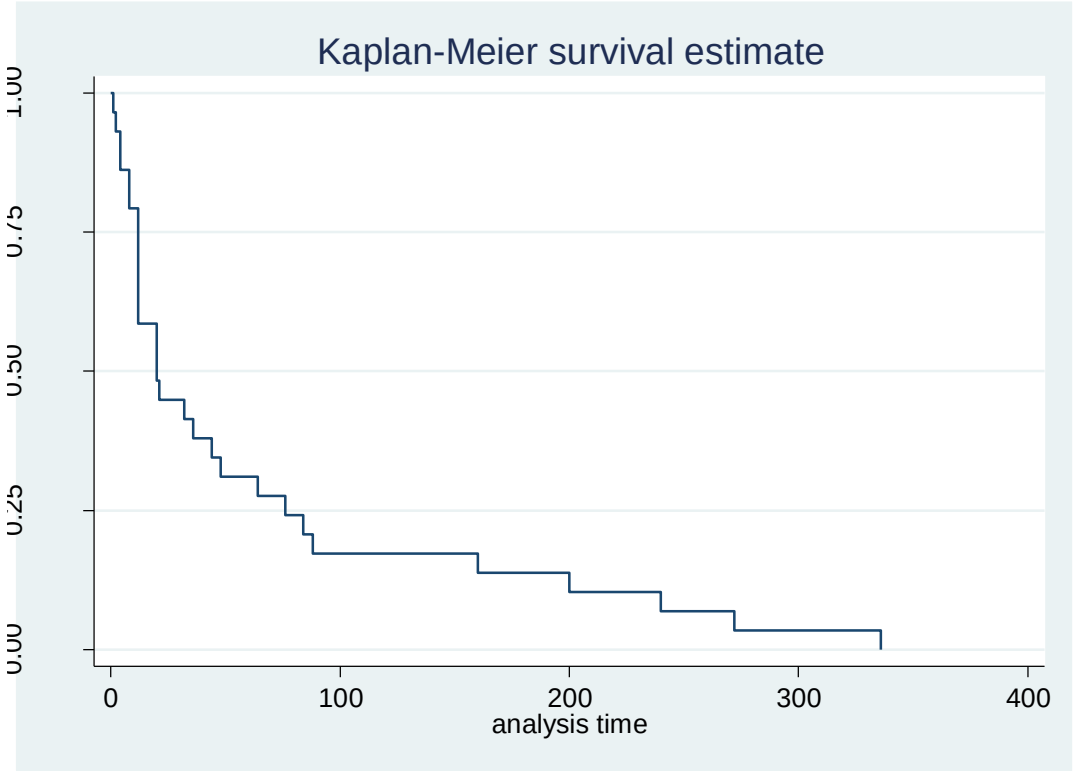


Figure 3.9: Kaplan Meier survival estimates of thirteen (13) women who only had surgery for carcinosarcoma with no radiotherapy. (Calculated from time of surgery until last time seen. The survival period is in weeks).

The survival of women at around 50 weeks (12.5 months) after surgery was just above 25% on these women. At a period of 100 weeks, the chance of survival drastically dropped to about 15% and continues to be low.

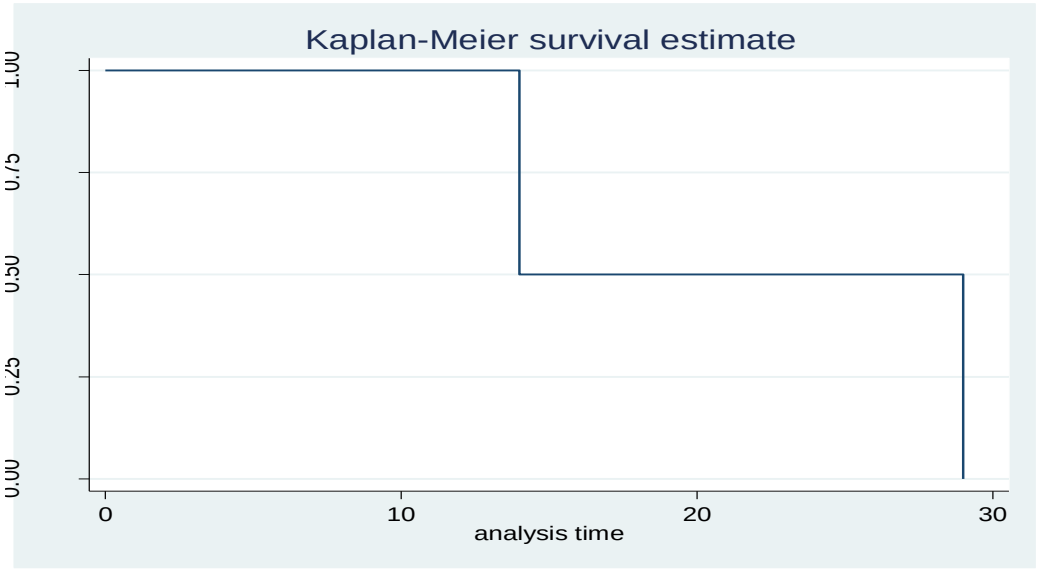


Figure 3.10: Kaplan Meier Survival graph of women who were treated with chemotherapeutic drugs calculated to last time seen. (Analysis time is in weeks)

The mean survival period on women who received Chemotherapy was 18.75 (SD± 13.35) weeks. The least survival period after chemotherapy was 2 weeks and longest was 30 weeks. Chemotherapy did not offer any survival benefit.

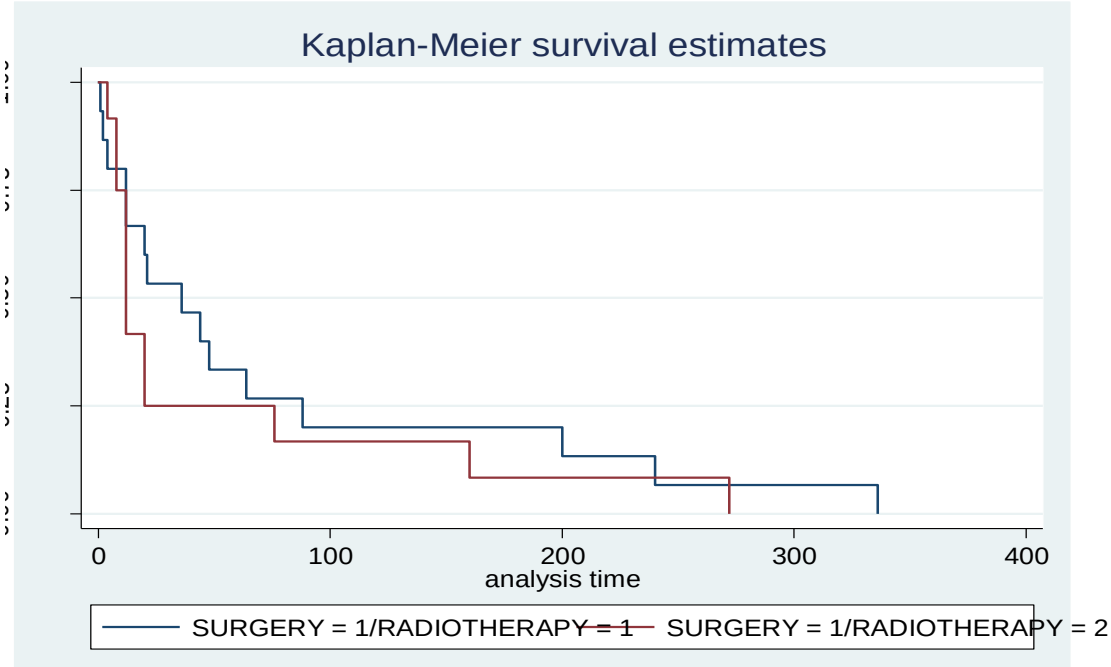


Figure 3.11: Kaplan Meier survival estimates comparing survival on women who underwent surgery alone and those who received radiotherapy after surgery. (The survival period is in weeks.)

There was no statistical difference in survival between the two groups. (women who had surgery alone and those who had surgery and adjuvant radiotherapy). This was observed until beyond 200 weeks. However, this was a low powered study.

The overall site of recurrence was as tabulated below.

Table 3.4. Common recurrence sites of Carcinosarcoma

SITE OF RECURRENCE	**N**	**%**
Vaginal Vault	4	36.36
Vault & Distant	1	9.09
Pelvic Cavity	0	0
Abdominal Cavity	2	18.18
Lymph nodes	0	0
Distal (Lungs, Brain etc)	3	27.27

CHAPTER 4: Discussion

Most women in our study were over the age of 60 years. Our findings were in keeping with current literature regarding the risk age for endometrial cancer in general and carcinosarcoma specifically. Endometrial cancer is common after the 6th decade of life. Rajanababu *et al* [37] in India reported the median age at presentation of 61.5 years (range 46–79 years). The available data also show that women with Carcinosarcoma are usually at the 5th decade of life, with most cases occurring between the sixth and seventh decade of life and have a median age of 62 years.[8,41] The mean age at diagnosis for carcinosarcoma in USA was 67 years (range, 23–85).[4]

Rajshekar and colleagues in their study, reported a median age of 56 years for their Indian study population and that 70% of them were at postmenopausal stage.[7] Of note is that the life expectancy for women in India is around 68.35 years.

There majority of women in our study (87.10%) were black, 9.68% were white and 1 (3.23%) was a coloured. These findings however need to be interpreted with caution as our study site/institution sees majority of African women in contrast to other races in South Africa. This was also not corrected to percentage population per race. Manzevora *et al* found that there was 19.6% African-American vs 80.4% non-African American of the women with carcinosarcoma. This could also relate to their population composition and distribution and not necessarily a burden of disease per race. However, they found a significant association between race and the AJCC stage at presentation: African Americans were more likely to present with a more advanced AJCC stage (II-IV) than non-African-American. It is also reported that the disease in black women recurred sooner with a PFS of 7.9 versus 14.2 months. The OS was also inferior in Black women with a median OS of 13.4 versus 30.8 months. [4]

The use of oral contraceptives is protective for endometrial cancer. Such protective effect is achieved at a mean 5 years of continuous use.[43] In our study, the mean use of contraceptives was 1.4 years. At this duration of use, the protective effects of contraceptives would not have been achieved. The mean Body Mass Index was 36.96 kg/m^2. This is considered obese. Endometrial cancer risk is increased in women who are obese.

The other risk factors associated with endometrial cancer in general (including the use of HRT, tamoxifen, cigarette smoking, and family history of malignancy) were not statistically significant in our study population. This may be due to a small study population.

Contrary to reports from most available literature, our study population presented commonly with abdominal distention (28.13%) compared with vaginal bleeding (6.25%). It is unclear why this cohort presented in this uncommon way. Abnormal vaginal bleeding is the commonest presenting sign in endometrial cancer. This unexpected presentation requires further validation in a prospective study. However, this could be due to recall bias as this was a retrospective study.

The correct diagnosis of carcinosarcoma was made in 84.38% of women and the commonest method was a biopsy of a mass in the vagina/through the cervical canal. This is contrary to common methodology in diagnosis of endometrial cancers which is by endometrial sampling. This is because carcinosarcoma unlike other endometrial cancers, present with a mass or polyp which is easier to collect tissue for diagnosis than in the endometrial cavity.

The mean number of collections to make a diagnosis was 1.18 times. This is unexpected as the tissues in the vagina/through the cervix are likely to be necrotic and hence less likely to yield conclusive results. Results were available in less than 6 weeks in 87.50% of the women. The period of less than 6 weeks in our setting although not optimum would be acceptable and results obtained after period of 6 weeks would be considered delayed.

The uterus size was assessed as more than 12 weeks in the majority of these women (71.88%). This is in keeping with most available literature. More than 50% of these women still had a mobile uterus when assessed pre-operatively. This was unexpected as women with endometrial cancer in general and carcinosarcoma specifically present late.

The commonest surgery done was a total abdominal hysterectomy without a lymphadenectomy (37.50%). This is not in keeping with FIGO protocol/recommendations on surgical management of endometrial cancers. However, the data collected included cases that were done 10 years ago where pelvic lymphadenectomy was not routinely done for endometrial cancer in our hospital. In a 2013 study, Anupama R and Kuriakose D found that 95% of women with carcinosarcoma had TAH/BSO and only 60% had pelvic and para-aortic lymphadenectomy as part of the staging surgery.[6] A recent study in USA showed a lower percentage (43%) of lymphadenectomy during staging surgery.[40] Although our rate of concurrent lymphadenectomy was low (6.250%), this recent study shows that even in

current period, lymphadenectomy is not commonly done even though it is recommended as part of surgical staging by the International Federation for Obstetrics and Gynecology. Surgery was completed in the majority (79.31%) of women and this finding was expected as majority of women were assessed as having a mobile uterus. The majority of women in the study had early (although incomplete as lymphadenectomy was not done in most patients) surgico-pathological stages 1&2(56.25%). Although this is common with endometrial carcinoma, it is an unexpected finding on our patients who presented commonly with abdominal distension as opposed to abnormal per vaginal bleeding. However, our findings are similar to what Rajanbabu *et al* [37] found. They reported findings of fifteen (75 %) patients who were Stage I and II, 20 % stage III disease and 5 % with stage IV disease. A study by Manzerova also found that early (stage 1) disease was about 70% (69.9%) of the women with carcinosarcoma.[4]

The commonest heterologous differentiation was rhabdoid differentiation. This finding was in keeping with current literature from Kanthan *et al* who found that rhabdomyosarcoma was the commonest (18%) followed by chondrosarcoma (10%).[8]

In our study population, women received radiotherapy (56.88%) for carcinosarcoma as per protocols of both the gynecological oncology and radiation oncology units. Of these women 86.67% received it as adjuvant therapy. The percentage of women who received radiotherapy was higher than most available literature.[40] Although literature indicate that the response from radiotherapy is very poor amid better than chemotherapy, our unit had not reviewed the survival of patients who received radiotherapy and hence continuation. Bosquet and colleagues' study on survival for carcinosarcoma patients who had multimodal treatment found that stage I patients managed with adjuvant RT did not experience an improved disease-specific survival as compared to patients not treated with (RT 72% vs. 49%, p=0.07) although the disease-free survival was improved (66% vs. 41%, p=0.04).[41]

The mean dose of 39.93Gy and mean 17.5 fractions are in keeping with most international protocols. Compliance to radiotherapy follow up was good and hence poor compliance could not be listed as reasons for poor response to treatment, disease recurrence and morbidity.

There was poor survival in patients who received therapy with only 30.77% surviving beyond 12 months (1 year). This is expected of carcinosarcoma patients although data from the United States shows survival to a mean of 42 months.

The commonest site of recurrence for women who had a recurrence was the vault. This finding supports available literature on recurrence for carcinosarcoma whether therapy was given or not. However, Dusenbery and colleagues found that for leiomyosarcoma, the first site of recurrence was distant, pelvic & abdominal, pelvic & distant, abdominal & distant, and pelvic (in descending order of recurrence rate).[5] This seeks to suggest that leiomyosarcoma has a distinct recurrence pattern different from carcinosarcoma.

The most common cause of death in women with carcinosarcoma is disseminated disease. In our study, dissemination of the disease was reported as the cause of death in 63.26%.

Cigarette smoking is a known risk factor for many oncological and non-oncological diseases. Although cigarette smoking is known to be protective of endometrial cancer,[44] our study found that women who do not smoke had a 20% chance of surviving more than 12 months after therapy than those who smoke. Perhaps the contributory factors to this finding is the co-morbid diseases and poor health status associated with chronic smoking.

Although women of African race are likely to present at late stages of diseases, we found that women of African race were 4 times likely to survive for 12 months after therapy than white and coloured women.

We found no difference in survival on women who were treated with surgery alone and those who received radiotherapy after surgery. However, women who received radiotherapy suffered adverse effects such as desquamation, diarrheoa, urinary incontinence and VVF. Menzerova found that a longer survival was observed in the group of patients who received adjuvant radiotherapy compared to those who did not [42 vs 22 months ($p<0.0001$)].[4]

It is known that carcinosarcoma poorly responds to radiotherapy compared to other endometrial carcinoma subtypes and hence our findings are not alarming.

Recurrence of the disease was common after 12 months and commonest site was the vault. This is in contrast with findings on women who received chemotherapy, radiotherapy, or combination in the USA 2017 study. Although these patients had a stage 1 disease, the key findings of this investigation were that stage I uterine carcinosarcoma had a disproportionally high risk of distant-recurrence.[40] Women with carcinosarcoma were found to die from complications associated with metastasis of the disease.

CHAPTER 5: Conclusion

Uterine Carcinosarcoma is not as common as other endometrial carcinomas. The disease generally has a poorer prognosis and literature reports its poor outcome whether surgery alone or surgery with radiotherapy and/or chemotherapy is instituted.

Women on our study presented with presumed early stage disease (1 and 2) (this was an incomplete surgical staging as lymphadenectomy was only done in two patients) and the most common heterologous differentiation was rhabdoid. There was no difference in survival on women who were treated with surgery alone and those treated with radiotherapy after surgery. The poor response was not related to specific dose, type of radiation therapy and poor compliance to the treatment program. Patients who were treated with radiotherapy had morbidity associated with complications of radiotherapy without any survival benefits.

In a resource restrained environment such as ours, perhaps the use of radiotherapy on patients with carcinosarcoma should be individualized to those patients who require symptoms relief and resources channeled to those with cancers that have an improved survival after radiation therapy.

CHAPTER 6: Strength and Limitations of the study

This was a retrospective study and naturally has limitations. The study was also conducted in one center and the study population limited to those women who were admitted for surgery at the Gynaecological Oncology unit even though some were not operated after admission. It was noted that some women could have been referred and presented directly to the radiotherapy unit from secondary hospitals within the province.

Although it is acknowledged that carcinosarcoma is a rare disease, over a period of ten years, the numbers that our research recruited was less than fifty. Our study population was small.

There were only 2 patients who received chemotherapy and hence their outcome of could not be well compared with the other two groups.

There was a lot of missing information on the patients' records which was omitted during clerking on admission. It was unknown whether all the women who were followed up until "last date seen" were still alive.

The study was extended over the period of 10 years. It was able to directly compare the patients who had surgery alone and those who had surgery and radiotherapy.

CHAPTER 7: Recommendations for Future Research and Clinical Practice

In this era of anti-angiogenesis drugs and use of hyperthermia (both radiotherapy and chemotherapy), it would be interesting to know if the use of such newer modalities will yield better outcome in overall survival and disease-free survival.

The role of nuclear medicine modalities such as Targeted Alpha Therapy (TAT) in carcinosarcoma has not been well explored. With such resources available in our healthcare system, a collaboration with relevant departments will yield much needed information and perhaps better hope for patients with uterine carcinosarcoma.

The findings of this study may be useful on further research on management of carcinosarcoma perhaps extended into larger multi-center study to obtain a reasonably representative picture on how the three treatment modalities perform.

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Annexure 1 : Data Collection Sheet

Demographic Data

Age (in years)													
Parity	0		1		2		3		4				
Race	Black		White		Indian		Chinese		Coloured		Unknown		
Educational level	No schooling		Primary school only		High school (no matric)				Matric		Tertiary		
Employment status	Unemployed				Self employed								
History of contraceptive use	COC		POP		Patch		Inject		IUD		Never		Unknown
Period on contraceptives(any)	<5yrs		5-10		>10 years								
Body Mass Index	Weight				Height				Score				

HIV status	Positive		Negative		Unknown							
If Positive,	CD4		VL		Period on ARVs							
Hypertension	Yes		No		Unkno							
Diabetis Mellitus	Yes		No		Unkno							
Postmenopausal period (in months) at diagnosis												
Previous use of HRT	Yes		No		Unknown							
Tamoxifen use previously	Yes		No		Unknown							
Other high risk drugs (specify)												
Smoking	Never		Current		Prior		Unkn					
Family history of Ca	Yes		No									
If yes, which organs system?												

Presenting symptoms at 1st consultation

Abnormal per vaginal bleeding			Abdominal distension								
Abdominal pain			Mass in the vagina								
Vaginal discharge			Weight loss								
Other (specify)			Unknown								
1st presentation (months)	<1		1-5		6-12		>12		Unknown		

Histological diagnosis (Pre surgery)

Period from specimen collection to results report (in months)	<6		6-8		8-10		10-12	
Number of times specimen collected	0nce		Twice		>2			
Biopsy method	Endosample		DD&C		Hystoroscopy			
Histological typing								

Pre-Surgery

Uterine size in weeks	<6 weeks		6-12 weeks		>12 weeks			
Mobility of mass/uterus	Fixed		Partially mobile		Mobile			
If there were chronic diseases, were they controlled?	Yes		No		Unkno		N/A	
ECOG/Functional status	1		2		3 or more			
Biochem/Hem markers	Albumin		Hb		Creatinine			
Ultrasound findings	Ascites		Omental cake		Hydronephrosis			
Chest X-ray findings	Pleural effusion		Infective changes		Solid Metastasis			

Surgery

Type done (Tick approp)	TAH	BSO	LND	Peritoneal Washings	Unknown			
Timing of surgery	Pre radiotherapy		Post radiotherapy		Unknown			
Diagnosis to surgery	<6 weeks		6-8 weeks		8-12 weeks			
Surgical staging	1 A / B	2	3 A /B / C 1, 2	4 A / B	unknown			
Complications of surgery	Bleeding	Visceral injury	Relook	Infection	None			
Other complications (DVT, PE, Nosocomial sepsis)								
Outcome of surgery	Abandoned		Completed		Unknown			
Histology Results								
Histological components incl/excl heterologous differentiation								

Immunohistochemistry (if any)								
Cytology results								
Hospitalization post op	3 days		4-7days		8-14 days		>14 days	

Radiotherapy

Type of radiation	Adjuvant				Neo adjuvant			
Diagnosis to radiation period	< 6 weeks				>6 weeks			
Presentation at MDT to DXT period	<6 weeks				>6 weeks			
Dose of radiation (in Gy) / Fractionation								
Number of cycles								
Compliance to radiotherapy treatment	Yes		No		Unknown			
Delays during DXT	Yes		No		Unknown			
Complications experienced after radiation	Yes		No		Unkn			
If Yes, which complications?								
Chemotherapy used	Yes				No			
If yes, drugs, dosages	Drug(s)				Dosages			
Complications of chemotherapy: Early								
Late								
Survival after radiation (months)	>12		6-12		3-6		<3		Unknown	
Post treatment Recurrence	6		6-12		>12		Unknown		None	
If yes, site of recurrence	Vault		Pelvis		Abdomen		Nodal		Distant	

Cause of death

Known		**Unknown**	

If known, what was the cause?

Medical conditions	
Wound complications	
Other infections (specify)	
Co-morbid diseases	
Dissemination of disease	

Annexure 2: Wits Human Research Ethics Committee Permission

R14/49 Dr Langanani Mbodi et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170945

NAME: (Principal Investigator)	Dr Langanani Mbodi et al
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The Outcome of Patints with Uterine Carcinosarcoma
DATE CONSIDERED:	29/09/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Prof A Woodiwiss, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/10/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting `the study was initially reviewed. In this case, the study was initially reviewed in September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES