Outcomes of carcinosarcoma in a tertiary care institution in India

Anne George Cherian, Anitha Thomas[1], Ajit Sebastian[1], Tunny Sebastian[2], Vinotha Thomas[1], Rachel G. Chandy[1], Abraham Peedicayil[1]

Abstract

Background: Carcinosarcoma is a rare malignancy, and reports are often mixed along with other sarcomas. The literature on uterine carcinosarcoma *per se* is sparse. **Aims:** This study aims to evaluate the demography, survival, and optimal treatment strategy of uterine carcinosarcoma. **Settings and Design:** A tertiary care center in India. The study design was descriptive with survival analysis. **Materials and Methods:** The medical records of all 18 patients admitted with uterine carcinosarcoma between January 2011 and December 2015 were reviewed. Baseline characteristics and outcomes were studied. Survival analysis was done using the Kaplan–Meier method and compared between treatment groups using the Log-rank test. **Results:** The total number of uterine malignancies operated in our center over this time period was 311 of which 18 were carcinosarcomas (5.7%). Median age of presentation was 61 years (36–77 years). Most women (94%) were postmenopausal and 67% of them presented with postmenopausal bleeding. Over half of the patients (56%) presented late (Stage III or IV). Only 11 (61%) had adjuvant treatment and 7 patients had expired at the time of follow-up. The median survival was 284 days (95% confidence interval 107–461). Patients who received adjuvant therapy did better compared to those who did not (P = 0.036). **Conclusions:** Carcinosarcomas are aggressive tumors of postmenopausal women who present with bleeding or discharge per vaginum. In spite of adequate surgical staging followed by adjuvant therapy, survival remains poor. Improvements in early detection and optimal therapy need to be made.

Key words: Carcinosarcoma, survival, treatment

Introduction

Carcinosarcoma uterus, previously known as malignant mixed mullerian tumor of the uterus is a rare, but aggressive uterine malignancy which usually presents in postmenopausal women. It comprises of about 1.5% of all uterine malignancies.[1] This malignancy usually presents as postmenopausal bleeding, discharge per vagina, abdominal mass or distension and occasionally as distant metastasis. The patients often have an enlarged uterus and may have tumor protruding through the cervix.

Carcinosarcoma is a biphasic tumor with malignant mesenchymal and epithelial components. Most carcinosarcomas appear to be monoclonal where the epithelial elements have undergone sarcomatous differentiation. Carcinosarcomas have a less favorable outcome compared to other uterine malignancies with 5-year-survival rates between 33% and 39%.[2] The primary treatment of carcinosarcoma is surgery; however, there is a high incidence of local and distant metastasis. Most recurrences develop within 1 year of therapy.[3] Current evidence suggests that adjuvant chemotherapy may be beneficial and that postoperative radiation therapy should be tailored according to the operative findings.

There are very few studies, especially in India, which have looked at carcinosarcomas, their treatment, and survival outcomes. Most studies, even in the world literature, have looked at all sarcomas clubbed together. The aim of this study was to look at clinicopathological features and outcomes of carcinosarcomas of the uterus in our center as well as identify predictors of survival.

Materials and Methods

Settings and design

This study was conducted at a tertiary care center in India. The study design was descriptive with survival analysis.

Participants

We did a retrospective analysis of all patients admitted with a diagnosis of uterine carcinosarcoma between January 2011 and December 2015.

Methods

The electronic medical records of all these patients were reviewed after clearance from the Institutional Review Board. Demographic data included were age at diagnosis, parity, menopausal status, presenting complaints, and treatment undertaken including details of surgery as well as adjuvant chemotherapy or radiation therapy received. Attempts were made to write to patients and contact them by telephone if they had not returned for follow-up.

Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) software (version 16.0, SPSS Inc, Chicago, IL, USA) and survival was calculated using the Kaplan–Meier method and comparisons made using the log-rank test. Survival was defined as the observed duration of life from the start of treatment to either the date of death or if living, the last date of contact.

Results

During this 5-year-period, we had 311 women with cancer of the uterus. Table 1 shows the different types of uterine malignancies diagnosed during this period. Among these, 18 had carcinosarcoma which accounts for 5.8% of all uterine cancers.

The median age of presentation was 61 (range 36–77) with a mean of 60.1 years (standard deviation 11.2). Table 2 shows the distribution of carcinosarcoma according to different age groups.

All of them were married, and only one patient had a history of infertility. Most women had more than five children. Distribution of women by parity is also shown in Table 2.

Among the 18 women, 17 were postmenopausal (94.4%) with a median of 7 years postmenopausal. Two women had a family

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/sajc.sajc_243_16

Departments of Obstetrics and Gynaecology, [1]Gynaecologic Oncology and [2]Biostatistics, Christian Medical College Hospital, Vellore, Tamil Nadu, India
Correspondence to: Dr. Anne George Cherian, E-mail: annegc97@yahoo.co.in

How to cite this article: Cherian AG, Thomas A, Sebastian A, Sebastian T, Thomas V, Chandy RG, *et al*. Outcomes of carcinosarcoma in a tertiary care institution in India. South Asian J Cancer 2018;7:31-3.

history of malignancy and 10 had some comorbidity. Most women had a BMI below 30 (84%) and presented in either Stage III or IV (56%) at the time of diagnosis. Most of the patients presented with postmenopausal bleeding (66.7%).

Treatments undergone by the patients are shown in Table 3. Seventeen patients underwent total abdominal hysterectomy with salpingo-oophorectomy. In addition, 15 women had omentectomy, 14 had pelvic lymph node dissection (PLND) while 12 had paraaortic lymph node dissection (PALND). One had undergone just a biopsy as she had stage IV malignancy which was inoperable. The proportion of metastatic disease was 4/15 (26.7%) of those who underwent omentecomy, 4/14 (28.6%) among those who underwent PLND, and 5/12 (41.7%) among those who underwent PALND. Two women with positive paraaortic nodes actually had negative pelvic nodes.

Eleven patients had adjuvant therapy of whom 10 had only combination chemotherapy while one had both chemotherapy and radiation therapy. Seven patients did not receive any adjuvant therapy either because they were too sick or because they defaulted.

Seven of the patients had died at the time of follow-up. All of them died within a year of initiating treatment. One was alive with recurrent disease. Among the seven who died, two were Stage I but did not receive adjuvant treatment in our hospital.

The median survival was 284 days (95% confidence interval [CI] 107.1–460.8) [Figure 1]. If stage I, median survival was 255 days (38–255); if Stage III, median survival was 211 days (57–1062), and for Stage IV, median survival was 241 days (203–284). Survival by stage at diagnosis did not show significant difference with $P = 0.593$.

Those who received chemotherapy showed a significantly higher survival than those who did not ($P = 0.036$) as shown in Figure 2.

Table 1: Types of uterine cancers (*n*=311)

Histology	*n* (%)
Carcinoma	276 (88.7)
Carcinosarcoma	18 (5.8)
Leiomyosarcoma	8 (2.6)
Endometrial stromal sarcoma	3 (1.0)
High-grade sarcoma	2 (0.6)
Others*	4 (1.3)

*Undifferentiated endometrial sarcoma, spindle-cell sarcoma

Table 2: Patient characteristics

Factor	*n* (%)
Age	
<50	3 (16.7)
50-59	5 (27.8)
>59	10 (55.5)
Parity	
0-1	3 (16.7)
2-4	8 (44.4)
>4	7 (38.9)
BMI	
19-24	7 (38.9)
25-30	8 (44.4)
>30	3 (16.7)
Presenting symptoms	
Postmenopausal bleeding	12 (66.7)
Discharge per vaginum	2 (11.1)
Abdominal pain/distension	2 (11.1)
Others	2 (11.1)
Stage at presentation	
Stage I	8 (44.4)
Stage II	0
Stage III	6 (33.3)
Stage IV	4 (22.2)

BMI=Body mass index

Table 3: Treatment of uterine carcinosarcoma

	n (%)
Surgery	
Biopsy only	1 (5.5)
Hysterectomy BSO	17 (94.5)
With omentectomy	15
With PLND	14
With PALND	12
Adjuvant treatment	11 (61.1)
None	7 (38.9)
Chemotherapy	10 (55.6)
Radiation + chemotherapy	1 (5.5)

BSO=Bilateral salpingo-oophorectomy, PLND=Pelvic lymph node dissection, PALND=Paraaortic lymph node dissection

Discussion

Carcinosarcoma of the uterus is a very aggressive tumor with poor prognosis. Its incidence starts increasing at 50 years of age and plateaus around 75 years of age. The median age of diagnosis is 62–67 years.[4] The most common etiological factor associated with this malignancy is exposure to radiation, and it has been suggested that these tumors will arise in an earlier age compared to when they arise *de novo*.[5] Other factors which have been associated with etiology of these tumors are use of tamoxifen, exogenous estrogen, obesity, and nulliparity.

We did a retrospective study to look at presentation and outcome of uterine carcinosarcoma. Since these tumors are considered akin to endometrial carcinomas, we did not mix them with other uterine sarcomas. Among all uterine malignancies at our institution, carcinosarcomas comprised of 5.8%, which was higher than expected. This probably reflects referral bias as we are a separate department of gynecological oncology within a tertiary level hospital.

Compared to other endometrial malignancies, carcinosarcomas are more likely to metastasize to lungs and lymph nodes.[6] The stage at which the malignancy is diagnosed also has prognostic importance.[7] About 35% of these tumors are not confined to the uterus at diagnosis, and most studies report a median survival of about 21 months.[8] Overall 5-year survival rates are 33%–39%.[2] Survival has not improved over the years despite

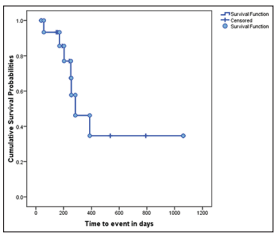

Figure 1: Kaplan–Meier graph showing the survival of the entire group of patients

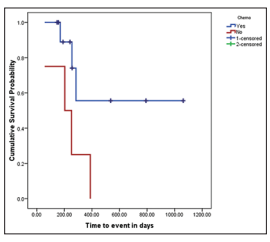

Figure 2: Kaplan–Meier graph showing the survival of patients who received chemotherapy (blue graph) compared to those who did not

different modalities of treatment. Outcomes in our patients have also been poor with median survival rates less than 1 year.

The most important prognostic factor associated with survival is the extent of the tumor at diagnosis.[9] In our series, the survival was similar across the stages probably due to noncompliance to adjuvant therapy.

Surgery is usually the principal modality of treatment.[10] Complete surgery involves abdominal hysterectomy, bilateral salpingo-oopherectomy with pelvic and paraaortic lymphadenectomy. This helps in staging the disease and in planning further treatment. In a prospective, multicenter gynecologic oncologic group study of carcinosarcomas, 61 out of the 301 (20%) patients with clinical Stage I and Stage II disease were reassigned to Stage III and Stage IV after pathological staging on the basis of lymph node metastasis.[11] The study also revealed a recurrence rate of 53%.

Optimal cytoreduction with pelvic node dissection has also been shown to have improved overall survival compared to suboptimal surgery.[12]

Postoperative treatment of carcinosarcomas has been debated, and a conclusion has still not been arrived at. Most patients have poor survival and a tendency to develop distant metastasis.[13] Brown *et al*. looked at early-stage carcinosarcoma managed surgically and administered vault brachytherapy. They found that they had high rates of local and distant relapses.[14] While others suggest that adjuvant pelvic radiation appeared to improve local control without much difference in overall survival,[4] a large retrospective study using the SEER database has shown definite benefits of radiation therapy following surgery compared to surgery alone with hazard ratio of 0.89 (95% confidence interval, 0.83–0.95; $P < 0.001$).[15]

Several chemotherapeutic agents have been tried over the years such as adriamycin,[16] cisplatin[17] and paclitaxel[18] with response rates <20%. Ifosfamide had a response of 32%–36%. Combination chemotherapy has the best response but has increased toxicity, especially if ifosfamide is used.[19,20] The chemotherapy agents most commonly used for uterine carcinsarcoma have been ifosfamide and paclitaxel although carboplatin and paclitaxel seem to be as effective with much less toxicity. Carcinosarcomas are treated-like carcinoma endometrium rather than the other uterine sarcomas.

Conclusions

Carcinosarcomas are aggressive tumors of postmenopausal women who present with bleeding or discharge per vaginum. Surgical staging and combination chemotherapy are the mainstay of treatment. In spite of adequate debulking followed by adjuvant therapy, survival remains poor. Improvements in early detection and optimal therapy need to be made.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol 2004;93:204-8.
2. Schweizer W, Demopoulos R, Beller U, Dubin N. Prognostic factors for malignant mixed müllerian tumors of the uterus. Int J Gynecol Pathol 1990;9:129-36.
3. Spanos WJ Jr., Peters LJ, Oswald MJ. Patterns of recurrence in malignant mixed müllerian tumor of the uterus. Cancer 1986;57:155-9.
4. Gadducci A, Cosio S, Romanini A, Genazzani AR. The management of patients with uterine sarcoma: A debated clinical challenge. Crit Rev Oncol Hematol 2008;65:129-42.
5. Meredith RF, Eisert DR, Kaka Z, Hodgson SE, Johnston GA Jr., Boutselis JG, *et al.* An excess of uterine sarcomas after pelvic irradiation. Cancer 1986;58:2003-7.
6. Amant F, Cadron I, Fuso L, Berteloot P, de Jonge E, Jacomen G, *et al.* Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. Gynecol Oncol 2005;98:274-80.
7. Wolfson AH, Wolfson DJ, Sittler SY, Breton L, Markoe AM, Schwade JG, *et al.* A multivariate analysis of clinicopathologic factors for predicting outcome in uterine sarcomas. Gynecol Oncol 1994;52:56-62.
8. Gadducci A, Sartori E, Landoni F, Zola P, Maggino T, Cosio S, *et al.* The prognostic relevance of histological type in uterine sarcomas: A cooperation task force (CTF) multivariate analysis of 249 cases. Eur J Gynaecol Oncol 2002;23:295-9.
9. Gonzalez Bosquet J, Terstriep SA, Cliby WA, Brown-Jones M, Kaur JS, Podratz KC, *et al.* The impact of multi-modal therapy on survival for uterine carcinosarcomas. Gynecol Oncol 2010;116:419-23.
10. Menczer J, Levy T, Piura B, Chetrit A, Altaras M, Meirovitz M, *et al.* A comparison between different postoperative treatment modalities of uterine carcinosarcoma. Gynecol Oncol 2005;97:166-70.
11. Galaal K, van der Heijden E, Godfrey K, Naik R, Kucukmetin A, Bryant A, *et al.* Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. Cochrane Database Syst Rev 2013;(2):CD006812. doi: 10.1002/14651858.CD006812.pub3.
12. Harano K, Hirakawa A, Yunokawa M, Nakamura T, Satoh T, Nishikawa T, *et al.* Optimal cytoreductive surgery in patients with advanced uterine carcinosarcoma: A multi-institutional retrospective study from the Japanese gynecologic oncology group. Gynecol Oncol 2016;141:447-53.
13. Galaal K, Kew FM, Tam KF, Lopes A, Meirovitz M, Naik R, *et al.* Evaluation of prognostic factors and treatment outcomes in uterine carcinosarcoma. Eur J Obstet Gynecol Reprod Biol 2009;143:88-92.
14. Brown LC, Petersen IA, Haddock MG, Bakkum-Gamez JN, Lee LJ, Cimbak NC, *et al.* Vaginal brachytherapy for early-stage carcinosarcoma of the uterus. Brachytherapy 2015;14:433-9.
15. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B, *et al.* Uterine sarcoma: Analysis of 13,089 cases based on surveillance, epidemiology, and end results database. Int J Gynecol Cancer 2016;26:1098-104.
16. Omura GA, Major FJ, Blessing JA, Sedlacek TV, Thigpen JT, Creasman WT, *et al.* A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer 1983;52:626-32.
17. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, *et al.* Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: A gynecologic oncology group study. J Clin Oncol 2004;22:3902-8.
18. Curtin JP, Blessing JA, Soper JT, DeGeest K. Paclitaxel in the treatment of carcinosarcoma of the uterus: A gynecologic oncology group study. Gynecol Oncol 2001;83:268-70.
19. Sutton G, Brunetto VL, Kilgore L, Soper JT, McGehee R, Olt G, *et al.* A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group study. Gynecol Oncol 2000;79:147-53.
20. Anupama R, Kuriakose S, Vijaykumar DK, Pavithran K, Jojo A, Indu RN, *et al.* Carcinosarcoma of the uterus-a single institution retrospective analysis of the management and outcome and a brief review of literature. Indian J Surg Oncol 2013;4:222-8.