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Project Title: Carboplatin and Paclitaxel versus Doxorubicin and Cisplatin for Carcinosarcoma of the Uterus: A historical cohort with control based on FIGO 2009 criteria from the University of Manitoba.

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Abstract:
Objectives: To compare two different chemotherapy adjuvant treatment regimens currently and previously used at CancerCare Manitoba for endometrial carcinosarcoma.
Methods: This is a retrospective analysis of 60 patients diagnosed with primary endometrial carcinosarcoma at CancerCare Manitoba from 1998-2008. The demographic characteristics, malignancy stage, presence of recurrent disease, and treatment type(s) utilized were studied. 37 patients were found to have received either carboplatin/paclitaxel or doxorubicin/cisplatin for carcinosarcoma, and were further analyzed to determine if there was a statistically significant difference in progression-free survival and overall survival between the two treatments. Kaplan-Meier curves were used to display progression-free survival and overall survival.
Results: 60.4% of patients presented with low-stage disease. No statistically significant difference in progression-free survival or overall survival between the two cohorts was found. Recurrence rate was 31.7%. The mean time to recurrence in the combined cohorts was 23.2 months. 16.7% of the patients had or were currently being treated with tamoxifen. 73.7% of patients having recurrence did not undergo lymph node dissections and 100% of patients with local recurrence were treated with vaginal vault brachytherapy.
Conclusions: Due to the rarity of this malignancy, multi-centre studies are warranted based on the data collected as sample sizes were too small for statistical significance. Further investigations towards optimizing treatment and understanding disease associations should be performed in the future to help better manage these patients and improve survival.

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Introduction:

Uterine malignancies are the most common gynecological malignancy.[1] Endometrial carcinosarcomas, a specific type of uterine cancer, represent <4% of uterine malignancies and are typically very aggressive with more than 50% recurring after primary surgical and adjuvant therapy.[2,3] Five-year disease-free survival rates are generally poor at 56%, 31%, 13% and 0% for stages I-IV respectively.[4] Traditionally, malignant mixed Mullerian tumors (MMMTs) or carcinosarcomas (CS) of the uterus have been classified as sarcomas; therefore adjuvant chemotherapy treatment for uterine carcinosarcoma has been similar to that directed against the aggressive uterine sarcomas.[5] As carcinosarcomas have biphasic cellular populations, much research has been undertaken to determine the cell of origin of these rare malignancies.[6] Through immunohistologic, epidemiologic, clinicopathologic and molecular genetic research, there has been a surge of evidence demonstrating the monoclonicity of carcinosarcoma indicating an endometrial origin. This suggests that endometrial CS should be classified as carcinomatous rather than sarcomatous. The sarcomatous component is thought to represent the de-differentiation of the carcinomatous component with the latter element driving the tumor.[7]

In addition to the aforementioned research, there is also a great deal of clinical evidence supporting this new classification. This includes lymphatic spread and metastatic disease being attributable to the carcinomatous component, lymph node metastasis occurring as frequently as in endometrial adenocarcinoma as well as a response rate to cisplatin as high as that in patients with endometrial adenocarcinoma.[7] Further evidence supporting the hypothesis that carcinosarcomas are actually metaplastic carcinomas include: frequent association of carcinosarcomas with otherwise typical endometrial adenocarcinomas within the same hysterectomy specimen, frequent recurrence of carcinosarcomas as pure adenocarcinomas, occasional recurrence of apparently pure endometrial adenocarcinomas as carcinosarcomas, and similar metastatic pattern of carcinosarcomas and endometrial adenocarcinomas (commonly through lymphatics whereas true sarcomas often metastasize hematogenously).[5,6,8,9]

Carcinomas arising in the endometrium can be divided into two types. Type 1 is typically associated with hyperestrogenism, obesity and hyperlimidemia. Type 1 has a well or moderately differentiated endometrioid histology and a good prognosis, and fortunately is the more common type of neoplasm.[10] Type 2 endometrial carcinomas are seen less frequently and are typically seen in women without these clinical features.[10] Type 2 have poorly differentiated endometrioid or serous histology, have a worse prognosis and are more often associated with *p53* mutations.[10] Endometrial CS are classified as Type 2 endometrial carcinomas with the epithelial component of the tumor most often resembling high grade endometrioid, serous or clear cell carcinoma.[10]

When comparing women with endometrial CS and endometrioid carcinoma, there are several differences. Recent studies have shown that endometrial CS presents in slightly older women (70 vs. 66 years; $P < 0.001$) and present with more advanced disease (41% vs. 31% having stage III/IV; $P < 0.001$).[10] Tamoxifen, a treatment that is beneficial to

women with estrogen receptor-positive breast cancer, increases the risk of developing endometrial carcinoma, especially Type 2 carcinomas.[10] As well, tamoxifen is thought to have a carcinogenic effect via a genotoxic pathway through DNA adducts leading to more patients having *p53* mutations in tumors related to tamoxifen use than those that have not been treated with tamoxifen.[11]

Endometrial carcinosarcomas have a high likelihood of spreading to pelvic and para-aortic lymph nodes and thus the optimal initial management of this malignancy is surgical staging including total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), lymph node dissections (LND), resection of any gross disease and pelvic washings.[12,13] Post-operative management, however, is not as clear. As patients typically present with Stage III or IV disease, systemic chemotherapy is often necessary after cytoreductive surgery.[14] There is no clear consensus, however, as to which chemotherapy regimen is best to treat patients with endometrial CS due to the fact that this malignancy is quite rare and randomized control trials are much more difficult with the consequently small sample sizes. For example, the Gynecology Oncology Group (GOG) conducted a randomized phase III trial testing the efficacy of whole abdominal radiation versus cisplatin-ifosfamide-mesna following surgery for patients with stages I-IV endometrial CS. The study took 11 years in order to achieve the number of participants necessary for the study to be significant.[15] Due to the small sample sizes, management of this aggressive malignancy often tends to be guided by clinical evidence rather than phase III trials.

From 1998-2002, patients treated at CancerCare Manitoba with endometrial CS received a combination of doxorubicin (Adriamycin) and cisplatin as this was considered standard first-line chemotherapy.[16] As evidence began to mount demonstrating the cellular origin of endometrial CS, oncologists began to re-evaluate the treatment for these aggressive tumors. As these tumors were beginning to be thought of as epithelially derived, chemotherapeutic agents active against endometrial carcinomas such as anthracyclines, the platinums, dacarbazines, taxanes and ifosfamide were thought to be effective in endometrial CS as well.[13] Although ifosfamide is effective against endometrial CS, especially when used in combination with cisplatin, it causes a great deal of morbidity and even mortality to patients and often cannot be tolerated.[2,17] In 1999, oncologists in B.C. began treating endometrial CS with carboplatin-paclitaxel because of its ease of administration and decreased side-effects compared to the agents in use at that time. This chemotherapy combination was being used for ovarian cancer and research into its efficacy on endometrial CS was warranted based on the fact that the tumors were newly being thought of as high-grade metaplastic adenocarcinomas as opposed to sarcomas.[17] The B.C. study determined that carboplatin-paclitaxel was at least 55% effective against endometrial CS and it was more convenient, less expensive and easier to deliver than the single-agent ifosfamide.[17] Toyoshima et al. demonstrated that carboplatin and paclitaxel had higher overall response rate and complete response rates than any other combination observed in previous studies; however the number of cases in the study were too small for statistical analysis.

The purpose of this study is to retrospectively compare the chemotherapy combination used prior to 2002 (doxorubicin and cisplatin) with the current standard of care at CancerCare Manitoba (carboplatin and paclitaxel). The progression-free survival (PFS) as well as overall survival (OS) will be determined for those treated with either chemotherapy regimen. As well, an analysis of various descriptors will be performed in order to elucidate more information about the presentation and characteristics of this rare malignancy.

Methods:

We conducted a retrospective chart review of patients with primary uterine carcinosarcoma treated at CancerCare Manitoba from 1998-2008. Patients were excluded from the comparison of the chemotherapy treatments if they were not treated with either chemotherapy regimen, if they did not receive a TAH/BSO or if they had incomplete medical records. The treatment protocol at this time was to offer patients adjuvant chemotherapy. The majority of excluded patients either declined chemotherapy or were unfit for therapy. However, all patients diagnosed with a uterine carcinosarcoma from 1998-2008 were included in descriptor analyses. Patient age at diagnosis, FIGO 2009 stage, patient demographics, treatment (chemotherapy and radiation), surgical variations, mode of recurrence detection, site of recurrence and previous treatment with tamoxifen were all included in descriptor analyses. REB and RRIC approval was acquired prior to the initiation of the review. Data was collected from patient medical charts from CancerCare in addition to the electronic chart system, Aria. Patients were re-staged based on FIGO 2009 criteria using surgical pathological reports issued from St. Boniface General Hospital, Health Sciences Centre, Victoria General Hospital, and The Grace General Hospital. The new staging classifies Stage I disease as being confined to the corpus uteri, Stage II disease as invading the cervical stroma, Stage III disease as involving local or regional spread of the tumor (vagina, parametrium, pelvic or para-aortic nodes for example) and finally Stage IV disease indicates distant metastases or bladder/bowel spread.[18]

The determination of patient outcomes such as date of recurrence, date of death or date of last follow-up was essential for this project. The cut-off point for data collection was June 30th 2011. This information was then used to calculate PFS as well as OS. The method by which recurrence was detected was also collected.

Statistical analysis was conducted by the Department of Epidemiology at CancerCare Manitoba. Progression-free survival (PFS) was defined as the time from the date of surgery to either recurrence or death or to the last follow-up date (whichever occurred first). Overall survival (OS) was defined as the time from date of surgery to either the date of last follow-up or date of death. The Kaplan-Meier method as well as the Log-rank test were used for testing significance. All of the analyses were performed using SAS 9.2.

Results:

The CancerCare Manitoba database revealed 60 patients with the diagnosis of endometrial CS. There was one additional patient that was found incidentally to have a carcinosarcomatous polyp during a TAH/BSO for a primary endometrial adenocarcinoma and therefore this patient was not included in our descriptor analyses. As there were 2 patients who were not surgical candidates for their endometrial CS (diagnosed using fine needle aspirate biopsy and vaginal punch biopsy) the total number of patients was reduced when calculating the percentage of patients having lymph nodes dissected as well as staging performed. Patient demographics are shown in Table 1. The mean age was 69±10 with a range of 46-92. At the point of data collection completion, 53.3% of patients were alive. The remaining 46.7% of patients died either of primary disease, disease recurrence, disease complications, other malignancies, or unknown causes, and 1 patient died of surgical complications. Recurrence was detected in 31.7% of the patients. Recurrence was detected by a variety of methods including CT scan (52.6% of detections), physical exam (26.3% of detections), biopsy (15.8% of detections) and ultrasound (5.3% of detections). The sites of recurrence were recorded as well as the treatment regimen each patient having recurrence underwent (see Table 2). Tamoxifen had been previously used or was concurrently being used as a treatment for breast cancer in a total of 10 patients (16.7%). In addition to the 10 women with breast cancer, there were 3 other patients that had been diagnosed with previous malignancies such as cervical and rectal cancer.

Of the 58 patients who received surgery, only 21 patients (36.2%) had lymph node dissections and thus had complete surgical staging. The remaining 63.8% were assumed node negative and were staged accordingly using FIGO 2009 criteria as previously mentioned. The majority of patients presented with low stage disease (I-II) at 60.4%, whereas 36.1% of patients presented with Stage III disease and only 3.4% of patients presented with Stage IV disease. The majority of patients (53.3%) received both chemotherapy and radiotherapy as adjunctive treatment for their disease (see Table 3). Chemotherapy alone (16.7%), followed by radiotherapy alone (15%) and no adjunctive treatment (15%) were also possibilities for all patients with endometrial CS. Patient choice was the predominant reason for having no adjunctive treatment.

Of the 19 patients who experienced recurrence of their primary malignancy, 14 (73.7%) did not have lymph node dissections during surgery (see Table 4). Vaginal vault brachytherapy as a treatment was used in 12 (63.2%) of patients who recurred. As well, there were 8 (42.1%) and 5 (26.3%) patients treated with carboplatin/paclitaxel and doxorubicin/cisplatin, respectively, that had recurrence of their disease. The mean time to recurrence was calculated using the combined data from patients in cohort A and B and was found to be 23.2 months.

Cohort A (carboplatin and paclitaxel) and Cohort B (doxorubicin and cisplatin) consisted of 23 patients and 14 patients respectively for a total of 37 patients. The minimum surgical requirement for inclusion in this study was a TAH/BSO, however some patients also received peritoneal washings for cytology, omental biopsies and lymph node dissections. As the variability was so great amongst surgical procedures only the baseline TAH/BSO and lymph node dissections were documented as they are relevant for staging

purposes. Patients being treated with either regimen of chemotherapy had a range of 1-7 cycles with the mode being 6 cycles (29 patients) delivered by IV. The number of cycles patients received was highly influenced by side effects, renal function and patient choice. Formal toxicity assessment was not a primary objective of this study; however it was noted that several patients experienced peripheral neuropathy (commonly attributed to carboplatin), nausea/vomiting, anemia and other hematological conditions. Chemotherapy was used as an adjuvant treatment in all patients with the exception of 1 patient who had neoadjuvant chemotherapy (due to extensive disease) followed by additional chemotherapy post surgery. Patients being treated with chemotherapy were also often treated with radiation as well (see Table 5). Vaginal vault brachytherapy was given at a standard dose of 1680 cGy (with a range of 1120-4600 cGy) in 3 fractions to 23 patients (62.2%), whole pelvis radiation was given at a standard dose of 5000 cGy in 25 fractions to 1 patient (2.7%), and vaginal vault brachytherapy plus whole pelvis radiation (range of 3000-5000 cGy) were given to 6 patients (16.2%). There were, however, 7 patients (18.9%) who did not receive any radiotherapy due to patient refusal or because of low stage disease. As well, patients may have received more radiotherapy as palliation for recurrence; however, this was not part of the initial adjunctive therapy and thus was not analyzed.

Kaplan-Meier curves were constructed to display OS and PFS (see Figures 1, 2 and 3). There was no statistically significant difference between the two cohorts for either PFS or OS. Median PFS as well as median OS could not be calculated based on the data available.

Discussion:

This study collected and interpreted data that spanned 10 years at CancerCare Manitoba, and yet the number of patients diagnosed with endometrial CS was only 60. The rarity of this malignancy makes it incredibly difficult to analyze and obtain statistical significance. The primary objective of this study was to compare the standard of care chemotherapy regimen prior to and after 2002. After enforcing the inclusion criteria for the study, a sample size of only 37 was achieved. Thus, unfortunately, the sample size was deemed too small in order to be able to adjust the survival curves for age and stage. The various descriptors collected from all patients diagnosed with primary endometrial CS provided some interesting insight into different clinical aspects of this malignancy and how it has been managed at CancerCare Manitoba.

The role of lymphadenectomy is integral for the proper surgical staging of endometrial CS and the determination of appropriate adjuvant therapy.[3,9,11-13] There have been several studies in the United States demonstrating the survival benefits for patients undergoing lymphadenectomy, however these results were not well controlled and the subject remains somewhat controversial.[7,11] In this study the number of patients receiving lymph node dissections was only 36.2%. A study done by Park et al. demonstrated that even without intra-operative evidence of gross extrauterine disease or lymph node enlargement, the incidence of pelvic and/or para-aortic metastasis was 31.7%. Additionally, the results from the study by Park et al. demonstrated the importance of

sampling both pelvic and para-aortic nodes. The significant number of occult lymph node metastases may demonstrate an increased need for lymph node dissections during surgery (if the patient can tolerate the added procedure); patients previously thought to have low stage intrauterine disease may, in fact, have lymph node metastases and appropriate adjuvant treatment would then be necessary.

One of the major obstacles in the treatment of endometrial CS is its propensity to recur and spread.[4] Adjuvant radiotherapy such as vaginal vault brachytherapy is used with the main objective of reducing the risk of developing local recurrence.[4,20] In this study, however, 12 (63.2%) patients had vaginal vault brachytherapy and still had recurrence of their disease. As well, of the 4 patients who experienced local vaginal recurrence, 100% were treated with vaginal vault brachytherapy (± chemotherapy) which may indicate that vault brachytherapy is inadequate as a sole treatment in the prevention of local recurrence. Sartori et al. reported recurrences that occurred early and at distant sites. Vault brachytherapy may provide some benefit in controlling local vaginal recurrence; however, it may not have a great effect on controlling distant site recurrences.[4] Conversely, systemic chemotherapy is used in an attempt to eliminate microscopic disease and hopefully prevent recurrence and metastases.[20] In this study, patients in both treatment cohorts experienced recurrence with 13 (68.4%) patients overall and 8 specifically treated with carboplatin/paclitaxel and 5 patients treated with doxorubicin/cisplatin. Of the 7 patients who experienced systemic recurrence, 6 were treated with chemotherapy which is interesting as chemotherapy is specifically utilized to prevent the malignancy from spreading systemically. The mean time to recurrence was calculated by combining the data from both cohorts A and B and was found to be 23.2 months. The median time could not be calculated as sample sizes were insufficient. Recurrence rates range in the literature from 29% (for low-stage disease) to over 50%.[2,3,9,12,20] The recurrence rate in this study, with an incompletely staged patient population that was uncontrolled for age and stage, was 31.7% which is well below what is commonly reported for this aggressive malignancy.[2,3] Another intriguing finding in this study was that 14 (73.7%) patients who had recurrence did not receive lymphadenectomies. As previously discussed, microscopic disease can exist in nodes that do not appear to be enlarged.[19] This high percentage of patients not receiving lymph node dissections affects complete surgical staging and subsequent adjuvant treatment decisions, and could be hypothesized to result in sub-optimal treatment of residual disease leading to eventual recurrence.

In many published studies, one of the prominent clinical features of endometrial CS is that it presents as advanced stage disease.[3,21,22] In this study, however, 60.4% of patients presented with Stages I and II disease at diagnosis. This could be attributed to a number of factors such as incomplete surgical staging contributing to a lower stage or earlier clinical detection by both physicians and patients. Stage is the most important prognostic factor for endometrial CS thus patients presenting with earlier stage disease should presumably have a better prognosis.[9,23] It is unfortunate that the sample size from this study was too small to adjust the survival curves for stage as it would have been interesting to see the results from such a large proportion of patients presenting with low

stage disease. Multi-center data collection would be necessary to obtain a large enough sample size and this could possibly be an area of further research.

Tamoxifen is a well known risk factor for the development of endometrial adenocarcinoma.[24] Additionally, several case reports have been published that potentially link tamoxifen use with the development of endometrial CS.[24-28] Tamoxifen is a well-known anti-estrogen drug used in the treatment of breast cancer albeit with the knowledge that it may contribute to malignancy due to its weak estrogenic action on the endometrium.[26] Case reports have been published detailing potential links between duration of tamoxifen use and incidence of endometrial CS however, once again the sample sizes are an issue and statistical analysis achieving significance is not feasible.[24-26] A study by Swerdlow et al., however, demonstrated with statistical significance that duration of tamoxifen use is strongly correlated with development of endometrial carcinoma; as well the odds ratio for the development of endometrial CS, mixed mesodermal tumors and sarcomas was 13.5 as compared to endometrial adenocarcinoma which was 2.1.[27] In this study 16.7% of patients presenting with endometrial CS had been or were currently using tamoxifen as a treatment for breast cancer. There have been small case reports published and retrospective reviews of patients treated with tamoxifen who subsequently developed endometrial CS, however, more data is necessary. As well, of the 10 patients with endometrial CS that had been previously treated with tamoxifen, 6 patients had recurrence of their disease. For future research, the 10 patients from this study could be analyzed to further reveal the correlation between tamoxifen use and the development of endometrial CS and recurrence.

There have been a limited number of phase III trials elucidating the best adjuvant treatment for endometrial CS. In 2000, the Gynecologic Oncology Group (GOG) published a phase III trial testing the effectiveness of ifosfamide ± cisplatin for endometrial CS.[29] Response rates were increased with statistical significance in patients with combination ifosfamide/cisplatin, however the difference in overall survival was not statistically significant compared to the single agent ifosfamide.[29] The toxicity, however, was substantial with many patients suffering from hematologic, gastrointestinal and central neurologic side effects associated with ifosfamide and combination ifosfamide and cisplatin.[29] A Phase II study evaluating carboplatin and paclitaxel in patients with recurrent or advanced disease had an overall response rate of 54%.[2] PFS and OS were 7.6 and 14.7 months whereas the ifosfamide-cisplatin from the GOG study had a PFS of 6 and OS of 9.4 months.[2,29] Hoskins et al. reported a response rate of 60% in their patients treated with carboplatin/paclitaxel for newly diagnosed endometrial CS. In addition to the increased response rate as compared to ifosfamide ± cisplatin, there are also reduced financial costs associated with the use of carboplatin/paclitaxel.[17] As well as having a superior PFS and OS, carboplatin/paclitaxel is associated with a great deal less toxicity than ifosfamide-cisplatin, thus making it more tolerable to patients and perhaps increasing the likelihood of patients completing all of the treatment cycles necessary.[2,29]

Cisplatin/doxorubicin vs. whole abdominal radiation was compared in a GOG phase III study on advanced endometrial carcinoma.[30] The study found a statistically significant difference in OS and PFS between the two cohorts as well as reporting a 13% increase in

5 year overall survival as compared to the whole abdominal radiation cohort.[30] However, there were significant toxicities with the use of cisplatin/doxorubicin.[30] A large number of patients experienced Grade 3 and Grade 4 hematological toxicities such as leukopenia, neutropenia and thrombocytopenia.[30] Additionally, doxorubicin/cisplatin is thought to have contributed to the deaths of 8 patients in this study.[30] Sartori et al. reported a 70% response rate to cisplatin/doxorubicin, however survival curves were similar between cisplatin alone vs. cisplatin + doxorubicin. Contrarily, in the phase II trial conducted by the GOG, carboplatin and paclitaxel had significantly less toxicity than cisplatin/doxorubicin.[2] The number of patients suffering from chemotherapy induced thrombocytopenia was reduced in addition to the number of patients suffering from high-grade leukopenia.[2] GI side effects were also reduced in patients receiving carboplatin/paclitaxel.[2,30]

Additionally, there is a growing trend of tumor drug resistance which may be playing a role in the effectiveness of current treatment. Matsuo et al. conducted in vitro drug resistance assays on endometrial and ovarian CS tumors comparing various chemotherapy treatments. Paclitaxel and doxorubicin were found to have the highest rates of extreme drug resistance in this study which may have implications for the future when deciding upon treatment options.[31] The findings of this study suggest that chemotherapy effectiveness can be predicted based upon the drug resistance of the tumor in the assay which could, in the future, be used to test treatments before initiating them.[20] Based on the available literature, there is a growing need for the conduction of phase III randomized trials using carboplatin/paclitaxel and other additional combination therapies as an adjuvant treatment for endometrial CS as there is a great need to improve not only the quality of treatment, but the availability of evidence as well.[16,32]

The specific aim of this study was to compare the PFS and OS of patients treated with either carboplatin/paclitaxel or doxorubicin/cisplatin. Unfortunately, with the small sample sizes, only a limited amount of information could be gleaned from the statistical analysis. The data could not be adjusted for age and stage and thus all patients were analyzed collectively. This may have affected the results obtained as there was no way to calculate the median PFS or OS for either cohort. As well, the data from this study demonstrated no statistically significant difference in either PFS or OS between the two cohorts. This may be the result of small sample sizes or it could be hypothesized that platinum containing agents have similar effectiveness on endometrial CS. Further studies may be necessary examining single-agent platinum therapy for early and advanced endometrial CS. Based upon the limited availability of evidence comparing these two different chemotherapy regimens, toxicities reported in the literature may be the driving factor for determining treatment choice. It is unfortunate that objective toxicity grading is not currently in standard use at CancerCare Manitoba as this study would have benefited from comparing the toxicities of the two regimens. For future studies, this may be an area that can be improved in order to further broaden the data that could be studied which may be used to guide treatment choice. There was a significant amount of data collected from all patients diagnosed with endometrial CS over the 10 year span and this has a great deal of potential for future research. Retrospective analyses from multiple treatment centers could compare patients based on age, stage, adjuvant radiation treatment and

chemotherapy treatments provided there are an adequate number of patients. This could provide a great deal more information about OS and PFS (properly adjusted for age and stage) in addition to characteristics of this malignancy and how it presents.

In summary, this study was not able to find a statistical significance in PFS or OS between patients treated with either carboplatin/paclitaxel or doxorubicin/cisplatin. The mean time to recurrence in the combined cohorts A and B was 23.2 months. Toxicities may play a role in deciding the best chemotherapy regimen for the patients. As well, there are many factors to consider when studying this rare malignancy such as previous tamoxifen use, lymph node dissections, radiation therapy, recurrence and stage. More research is warranted based on this study's findings to further understand this rare malignancy, its risk factors and how it can be optimally treated.

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Figure 1: Kaplan-Meier curve of progression-free survival for carboplatin/paclitaxel cohort and doxorubicin/cisplatin cohort.

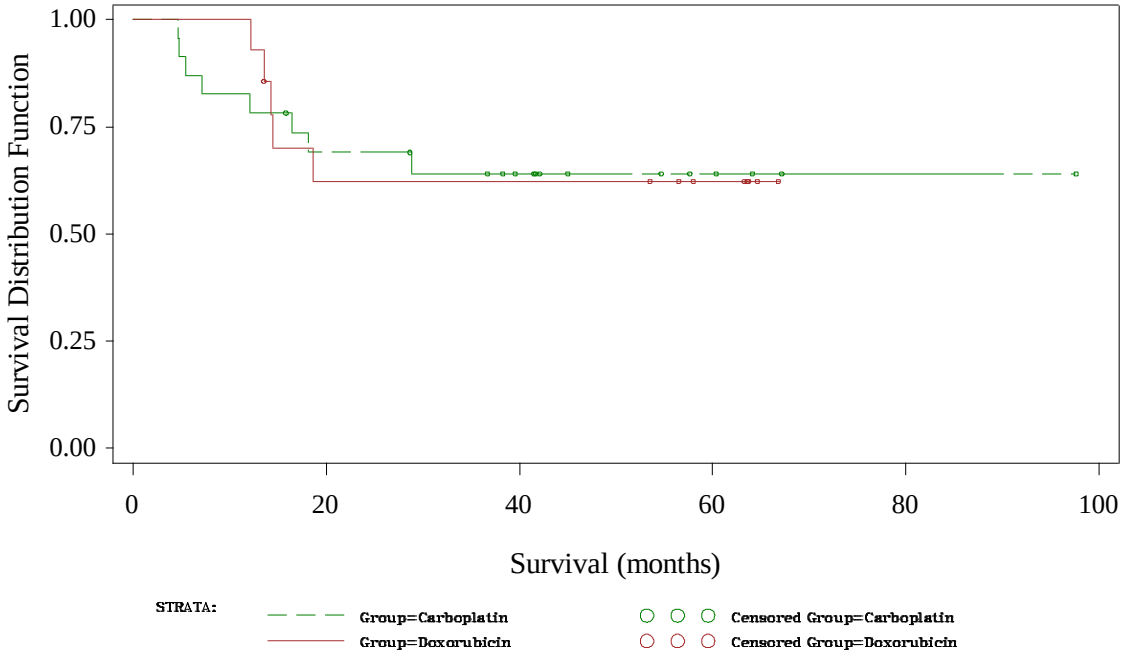

Figure 2: Kaplan-Meier curve for overall survival comparing carboplatin/paclitaxel cohort with doxorubicin/cisplatin cohort.

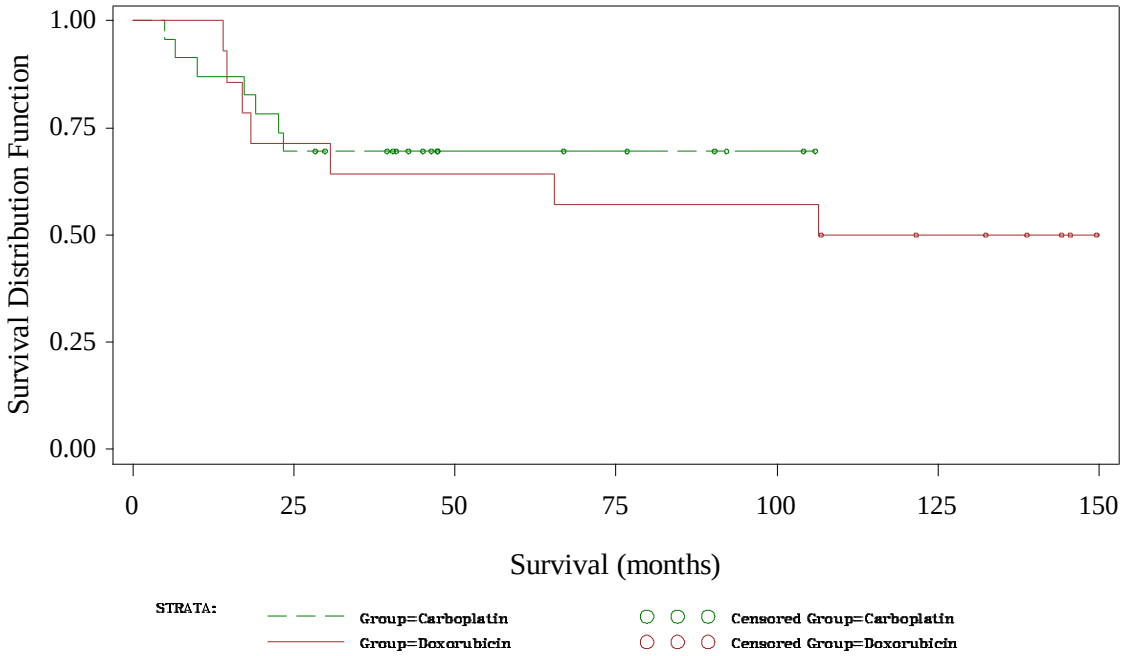

Figure 3: Kaplan-Meier curve of progression-free survival and overall survival of both cohorts combined

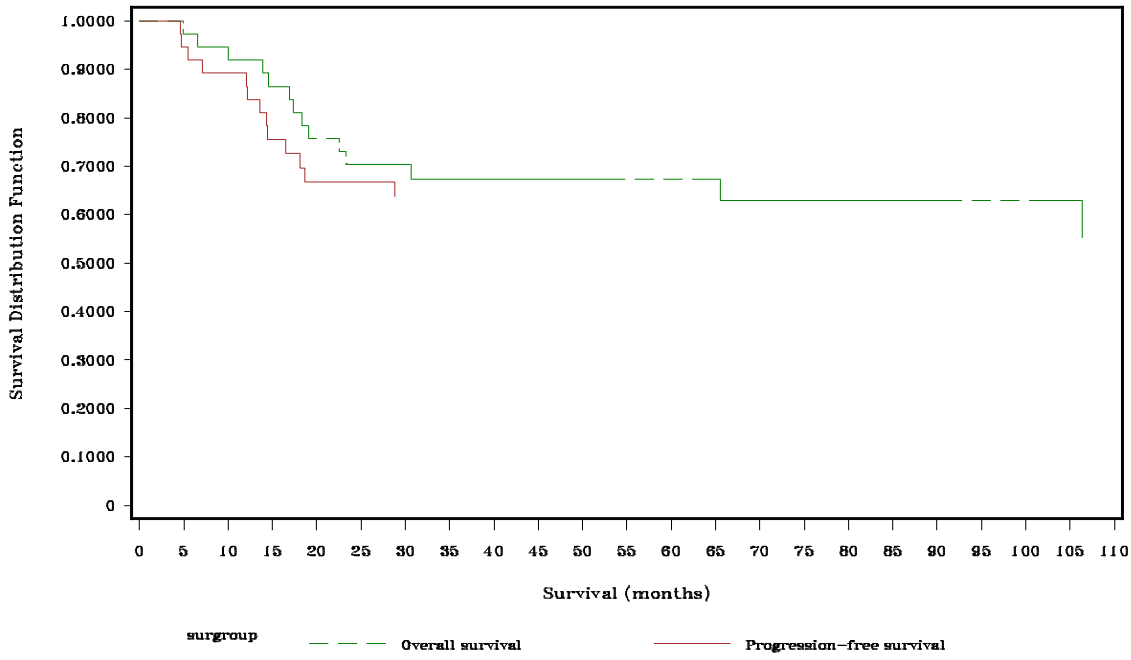

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Table 1: Patient demographics and summary of surgical treatments

Patient Demographics	*N* (=60 patients)	%
Age at Diagnosis, years		
Median (mean)	69 (69)	
Range	46-92	
Vital Status		
Alive	32	53.3%
Dead	28	46.7%
Recurrence Status		
Recurred	19	31.7%
Not Recurred	41	68.3%
Recurrence Detection	*N* (=19 patients)	
CT scan	10	52.6%
Ultrasound	1	5.3%
Biopsy	3	15.8%
Physical Exam	5	26.3%
Lymph Node Dissection (pelvic and/or para-aortic)	*N* (=58 patients)	
Nodes Dissected	21	36.2%
Nodes Not Dissected	37	63.8%
Previous Tamoxifen Use		
Yes	10	16.7%
No	50	83.3%
FIGO Stage	*N* (=58 patients)	
IA	20	34.5%
IB	8	13.8%
II	7	12.1%
IIIA	13	22.4%
IIIB	2	3.4%
IIIC1	6	10.3%
IIIC2	0	0%
IVA	0	0%
IVB	2	3.4%

Table 2: Patterns of first recurrence

Site of Recurrence	Chemotherapy + Vaginal Vault Brachytherapy *N*(=12)	Vaginal Vault Brachytherapy alone *N*(=2)	Chemotherapy Alone *N*(=2)	Whole Pelvis Radiation *N*(=2)	None *N*(=1)
Vagina	2	2	0	0	0
Pelvis	4	0	2	1	1
Systemic (lungs, liver and other distant sites)	6	0	0	1	0

Table 3: Summary of adjuvant patient treatments

Treatment Type	*N* (=60 patients)	%
Chemotherapy and Radiation	32	53.3%
Chemotherapy	10	16.7%
Radiation	9	15%
No Adjuvant Treatment	9	15%

Table 4: Adjuvant and surgical treatments patients received who subsequently developed recurrence

Adjuvant/Surgical Treatment	*N*(=19 patients)	%
Vaginal Vault Brachytherapy	12	63.2%
Carboplatin and Paclitaxel	8	42.1%
Doxorubicin and Cisplatin	5	26.3%
No nodes dissected	14	73.7%

Table 5: Radiation therapy types in patients treated with either regimen of chemotherapy

Radiation Treatment	*N* (=37 patients)	%
Vaginal Vault Brachytherapy	23	62.2%
Whole Pelvis Radiation (WPR)	1	2.7%
Vaginal Vault + WPR	6	16.2%
None	7	18.9%

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