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Original Research

# Efficacy and safety of carboplatin plus paclitaxel in gynecological carcinosarcoma: a Brazilian retrospective study

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*Objective*: To evaluate the efficacy and toxicity profile of carboplatin and paclitaxel (CP) in women with gynecological carcinosarcoma. *Methods*: This is a single-center retrospective study that included 64 women with stage I–IV gynecological carcinosarcoma treated with CP between January 2012 and December 2017. Patient demographics, tumor characteristics, toxicity, and survival outcomes, such as clinical benefit rate (CBR), progression-free survival (PFS) and overall survival (OS) were evaluated. *Results*: The median age was 65.2 years. Most patients were stage III–IV (73.5%) and had undergone surgery as initial treatment (95.3%). Optimal cytoreduction (R0) was associated with better median PFS ($P$ = 0.011) and OS ($P$ = 0.019) as compared to suboptimal cytoreduction (R1/R2). The CBR after first-line palliative CP was 36.7% (6.7% of complete response, 3.3% of partial response, and 26.7% of stable disease). For the general population, the median PFS was 11 months (95% confidence interval, CI: 8–50), and the median OS was 26 months (95% CI: 12-not reached, NR). The most common adverse event was anemia observed in 71.8% of patients. *Conclusion*: This study suggests that CP may be an effective and safe option with a more convenient schedule for treating gynecological carcinosarcoma.

*Keywords*

Gynecological carcinosarcoma; Uterine malignant mixed Mullerian tumor; Carboplatin; Paclitaxel; Chemotherapy

## 1. Introduction

Gynecological carcinosarcomas, also known as malignant mixed Mullerian tumors, are overly aggressive metaplastic high-grade carcinomas featured by carcinomatous and sarcomatous elements. With this biphasic histology, these tumors have been proposed as a model for epithelial-mesenchymal transition, a process characterized by a functional change facilitating migration and metastasis in many types of cancer. However, some evidence shows that the tumor arises from a common malignant clone [1, 2]. The most common disease site is the uterus, however there are rare occurrences in the cervix, fallopian tubes, and ovaries [3].

There is no Brazilian data regarding gynecological carcinosarcomas, but the incidence of uterine carcinosarcomas (UC) in the United States is lower than 2 per 100,000 women per year, accounting for less than 5% of all uterine cancers [4]. UC is typically diagnosed in postmenopausal women with a median age of over 60 years [5, 6]. Moreover, the risk of developing the disease is higher among African-American women [7–9].

Upfront surgery is the standard approach to early-stage disease [10, 11]. The positive survival impact of optimal cytoreduction was reported in a cohort of patients with advanced UC [12]. For IB to IV stage disease, the use of adjuvant chemotherapy was considered more beneficial than that of whole abdominal irradiation (WAI), as shown by the Gynecologic Oncology Group (GOG) 150 study results, in which the use of cisplatin, ifosfamide, and mesna (CIM) has been suggested to be effective and well-tolerated [13, 14].

Carboplatin plus paclitaxel (CP) regimen has been proposed as an alternative in the adjuvant and palliative setting. According to the National Comprehensive Cancer Network guidelines, CP is currently considered one of the regimens of choice for the treatment of UC [15]. The GOG 261, a phase III trial for patients with stage I–IV uterine or ovarian carcinosarcomas, recently reported some results suggesting CP as non-inferior to paclitaxel plus ifosfamide (PI) for progression-free survival (PFS) and overall survival (OS), with similar quality of life (QoL) score and neurotoxicity [16]. As for the approach to metastatic or recurrent disease, some phase II studies have demonstrated the efficacy and safety of CP as first-line therapy [17, 18].

Considered to be a well-tolerated regimen with a more convenient administration schedule as compared to the former ones, CP has been incorporated into the local routine as a standard adjuvant or palliative chemotherapy for patients with gynecological carcinosarcomas. However, data from pragmatic studies are scarce. This cohort study provides an opportunity to report our institutional experience as real-world evidence over the last six years emphasizing clinical response, toxicity and survival.

## 2. Material and methods

### *2.1 Patient selection and data collection*

This study was approved by the local Ethics in Human Research Committee and was conducted following the Good Clinical Practice Guidelines.

To evaluate toxicity, response rates (RR), PFS, and OS, an analysis of women with gynecological carcinosarcoma treated with CP as an adjuvant and/or first-line palliative chemotherapy at the Brazilian National Cancer Institute (INCA), between January 2012 and December 2017, was performed. Patients were identified through the internal database.

Patients who either had prior surgical or systemic treatment performed outside INCA, synchronic tumors, other histopathological diagnoses than gynecological carcinosarcoma or did not have any histological sample evaluated by a pathologist of the current study, were excluded from this cohort.

Clinical data regarding sociodemographic aspects, staging, surgery type, resection margin status, histological subtype, chemotherapy, and treatment toxicity were retrospectively obtained in the medical records. The clinical-stage at diagnosis was assigned based on the International Federation of Gynecology and Obstetrics (FIGO) 2017/TNM staging AJCC UICC 8th edition.

Women with operable disease underwent primary surgery and received CP with or without adjuvant radiotherapy and those with inoperable or recurrent disease underwent upfront palliative CP. Clinical response was assessed in patients with measurable disease using the radiological criteria based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [19]. The objective response rate (ORR) comprises complete response (CR) and partial response (PR). The clinical benefit rate (CBR) was defined by ORR plus stable disease. The adverse events were recorded at every cycle at the time of the visits, extracted by chart review and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [20].

### *2.2 Treatment*

The CP regimen consisted of paclitaxel 175 mg/m$^2$ over 3 hours plus carboplatin at an area under the curve (AUC) of 5 over 1 hour, both administered intravenously on day 1, every 3 weeks. Premedication following local protocols preceded intravenous paclitaxel administration. Treatment doses were adjusted or delayed at the discretion of physicians according to toxicities and the clinical aspects. The regimen was administered up to 6 cycles or stopped earlier due to prohibitive/limiting toxicities or disease progression. All patients had a complete medical history, physical examination, and laboratory tests before each treatment cycle, to evaluate adverse events. Some patients underwent adjuvant CP and had late disease recurrence (>6 months), having been re-exposed to CP as first-line palliative chemotherapy.

### *2.3 Statistical analysis*

PFS was calculated from the date of first CP infusion to the earliest date of disease progression, recurrence or death from any cause. OS was calculated from the first CP infusion to the date of death of any cause or censored if the patient was known to be alive on the last day of data collection. The Kaplan-Meier method was used to estimate PFS and OS. Patients were stratified by variables such as staging, histological subtype, lymphovascular invasion (LVI), surgical margin status, lymphadenectomy, omentectomy, and body mass index (BMI). The crude Hazard Ratio (HR) for each variable was calculated by the Cox proportional hazards. All variables associated with survival outcomes at $P$-value $< 0.20$ on univariate analysis were included in multivariate models. The Akaike criteria [21] was used to pick the most suitable model for multiple Cox analysis. A $P$-value of 0.05 or less was considered statistically significant. The missing data was excluded from the analysis. The statistical analyses were conducted using R environment [22].

## 3. Results

A total of 64 patients were included and the main characteristics of the patients are summarized in Table 1. The mean age of patients at diagnosis was 65.2 years (standard deviation, SD 7.9) and the primary sites were endometrium (92.2%), ovaries (6.2%), and cervix (1.6%). They were mostly mixed-race (43.8%) and had a BMI of more than 30 kg/m$^2$ (40.6%). The stage distribution at diagnosis was: stage I and II-26.6% (n = 17); III-43.8% (n = 28); IVA-4.7% (n = 3); IVB-25% (n = 16). With 29.7% of missing data, the heterologous subtype was more frequent (51.6%) than homologous (18.8%). LVI was observed in 26 (40.6%) cases, however there is no data for 21 (32.8%) patients.

Most patients (95.3%) underwent upfront surgery as described in Table 2. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) were performed in all surgical procedures. Lymphadenectomy was carried out in 40 patients (65.6%) and omentectomy, in 31 patients (50.8%). Optimal resection (R0) was successfully achieved in 68.9% of all cases that had undergone surgery.

Eighteen patients treated in the adjuvant setting had a recurrence, 13 of which were in a distant site. Eleven patients who underwent optimal cytoreduction did not undergo adjuvant chemotherapy because they were considered to be low-risk with early-stage disease, or due to prohibitive comorbidities, or even due to extended complications in the post-operative period. These patients were treated with first-line

**Table 1. Patient and histopathologic characteristics.**

| Characteristics | n = 64 | % |
|---|---|---|
| Age | | |
| Mean (SD) | 65.2 (7.9) | |
| Range | 38.2-81.8 | |
| Postmenopausal | 61 | 95.3 |
| Race | | |
| Mixed | 28 | 43.8 |
| Black | 18 | 28.1 |
| White | 17 | 26.6 |
| Missing | 1 | 1.5 |
| BMI | | |
| Mean kg/m$^2$ (SD) | 28 (6.4) | |
| $\geq$30 kg/m$^2$ | 26 | 40.6 |
| FIGO stage | | |
| I and II | 17 | 26.6 |
| III | 28 | 43.8 |
| IVA | 3 | 4.7 |
| IVB | 16 | 25 |
| Primary site | | |
| Endometrium | 59 | 92.2 |
| Ovaries | 4 | 6.2 |
| Cervix | 1 | 1.6 |
| Histologic subtype | | |
| Heterologous | 33 | 51.6 |
| Homologous | 12 | 18.8 |
| Missing | 19 | 29.7 |
| LVI | | |
| Yes | 26 | 40.6 |
| No | 17 | 26.6 |
| Missing | 21 | 32.8 |

BMI, Body mass index; LVI, Lymphovascular Invasion; SD, Standard deviation.

**Table 2. Treatment characteristics and tumor response.**

| Characteristics | n = 64 | % |
|---|---|---|
| Primary surgery (TAH + BSO) | 61 | 95.3 |
| Lymphadenectomy | 40 | 65.6 |
| Omentectomy | 31 | 50.8 |
| Surgical margin status | | |
| R0 | 42 | 68.9 |
| R1 | 3 | 4.9 |
| R2 | 16 | 26.2 |
| Adjuvant CP | 34 | 100.0 |
| Number of cycles | | |
| Mean (SD) | 5.6 (1.2) | |
| Range | 2–6 | |
| Site of recurrence | | |
| Local | 5 | 14.7 |
| Distant | 13 | 38.2 |
| First-line palliative CP | 30 | 100.0 |
| Upfront chemotherapy | 19 | 63.3 |
| Salvage post-progression chemotherapy | 11 | 36.7 |
| Number of cycles | | |
| Mean (SD) | 5.3 (1.5) | |
| Range | 1–6 | |
| Site of progression | | |
| Local | 11 | 36.7 |
| Distant | 7 | 23.3 |
| Local + distant | 4 | 13.3 |
| Tumor response | | |
| Complete response | 2 | 6.7 |
| Partial response | 1 | 3.3 |
| Objective response | 3 | 10.0 |
| Stable disease | 8 | 26.7 |
| Clinical benefit rate | 11 | 36.7 |
| Progressive disease | 19 | 63.3 |
| Radiotherapy | | |
| Adjuvant | 15 | 62.5 |
| Palliative | 9 | 37.5 |
| Treatment type | | |
| EBRT | 16 | 69.6 |
| EBRT + BCT | 7 | 30.4 |

BCT, Brachytherapy; BSO, Bilateral salpingo-oophorectomy; CP, carboplatin and paclitaxel; EBRT, External Beam Radiotherapy; R0, no cancer cells are seen microscopically at the primary tumor site; R1, cancer cells present microscopically at the primary tumor site; R2, Macroscopic residual tumor at primary cancer site or regional lymph nodes; SD, Standard deviation; TAH, Total abdominal hysterectomy.

palliative CP at the first signs of disease progression. In the palliative setting, disease progression occurred in 22 patients, of which 50% was locoregional. As for the 30 women with metastatic measurable disease, the CBR was observed in 11 (36.7%) patients, 2 (6.7%) with CR, 1 (3.3%) with PR and 8 (26.7%) with stable disease. Progressive disease was seen in 19 patients (63.3%) (Table 2). The radiotherapy was administered to 24 patients, 15 of them in the adjuvant setting (62.5%). External beam radiotherapy (EBRT) was the treatment of choice for 16 patients (69.6%) and 7 patients (30.4%) also underwent brachytherapy (Table 2).

The treatment-related toxicities are summarized in Table 3. The most frequent adverse events were hematological and gastrointestinal. Anemia was observed in 71.8% of the cases, mostly as grade 1 (31.2%) and grade 2 (29.7%). Neutropenia was present in almost half of the patients (45.4%), especially grades 3 (18.8%) and 4 (9.4%), with two cases of febrile neutropenia (3.2%). Nausea was reported by 60.9% of patients. There was no serious life-threatening toxicity and no patients died from treatment.

As shown in the Kaplan-Meier curves (Fig. 1), with a median follow-up of 37 months (95% confidence interval, CI: 31–48), the median PFS for the general population was 11 months (95% CI: 8–50). As summarized in Table 4, by univariate analysis, women with stage III–IV disease showed lower median PFS versus those with stage I–II (8 months versus 52 months, crude HR 2.37, 95% CI: 1.09–5.17, $P = 0.030$), as well as patients undergoing suboptimal resection versus optimal resection (R1/R2 versus R0, crude HR 4.48, 95% CI: 2.29–8.77, $P < 0.001$). On the other hand, lymphadenectomy

**Table 3. Treatment-related adverse events in patients treated with adjuvant and/or palliative chemotherapy (%).**

| Adverse event | Grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Renal injury | 4.7 | 0 | 0 | 0 |
| Mucositis | 18.8 | 1.6 | 0 | 0 |
| Fatigue | 39.1 | 12.5 | 4.7 | 0 |
| Nausea | 45.3 | 15.6 | 0 | 0 |
| Vomiting | 15.6 | 4.7 | 3.1 | 0 |
| Diarrhea | 10.9 | 1.6 | 0 | 0 |
| Constipation | 26.6 | 6.2 | 0 | 0 |
| Anemia | 31.2 | 29.7 | 10.9 | 0 |
| Neutropenia | 3.1 | 14.1 | 18.8 | 9.4 |
| Febrile Neutropenia | NA | NA | 1.6 | 1.6 |
| Thrombocytopenia | 28.1 | 3.1 | 0 | 0 |
| Myalgia | 26.6 | 9.4 | 1.6 | 0 |
| Joint pain/arthralgia | 10.9 | 0 | 0 | 0 |
| Peripheral neuropathy | 28.1 | 9.4 | 3.1 | 0 |
| Aminotransferases elevation | 7.8 | 1.6 | 0 | 0 |

NA, not applicable.

reduced the risk of progression by 65% (crude HR 0.35, 95% CI: 0.19–0.67, $P = 0.001$). Following the Akaike criteria, the final model chosen for multivariate PFS analysis consisted of four variables. Only suboptimal surgery was associated with a higher risk of progression and/or death (adjusted HR 3.09, 95% CI: 1.29–7.45, $P = 0.011$).

The median OS for the general population of the study was 28 months (95% CI: 15-not reached, NR) (Fig. 2). As shown in Table 4, patients with a more advanced stage had a lower median OS (stage III–IV versus I–II, crude HR 2.64, 95% CI: 1.09–6.43, $P = 0.032$), as too did the patients undergoing suboptimal surgery (R1/R2 versus R0, crude HR 4.36, 95% CI: 2.17–8.75, $P < 0.001$). In turn, lymphadenectomy reduced the risk of death by 73% (crude HR 0.27, 95% CI: 0.14–0.52, $P < 0.001$). Of the four variables present in the final model for multivariate OS analysis, only suboptimal surgery showed a significant association with the risk of death (adjusted HR 3.30, 95% CI: 1.21–9.01, $P = 0.019$).

## 4. Discussion

According to the data evaluation of the 64 women included, CP can be considered effective and safe for the treatment of gynecological carcinosarcoma. Optimal surgery can significantly increase both PFS and OS. Prospective randomized trials are difficult to carry out in this scenario due to low recruitment and, as a result, cohort studies may represent an alternative strategy for assessing new systemic treatment approaches.

It is well known that upfront surgery exerts a crucial role in the management of operable disease [15]. In a retrospective cohort by Tanner *et al.* [12], it was suggested that optimal cytoreduction was associated with better survival compared with patients that remained with residual disease after resection (median OS 52 versus 9 months, $P < 0.0001$). Furthermore, lymphadenectomy was strongly associated with better OS in women with gynecological carcinosarcoma through a population analysis using SEER data [10]. In the current study the vast majority of patients underwent resection with R0 surgical margins, which favorably influenced the median PFS and OS. However, this variable could not be included in the chosen final model for multiple Cox analysis. Unfortunately, systematic lymphadenectomies were performed in a small number of patients, which may have impaired the more accurate surgical staging of the patients included in the study. Some patients with diseases, initially considered as early-stage, were reclassified as stage IV during debulking surgery after the peritoneal disease was detected.

LVI plays an important role in determining prognosis in other settings of gynecological tumors [23]. In a study conducted by Matsuo *et al.* [24], it was described that the LVI in the sarcomatous component of gynecological carcinosarcoma was independently associated with decreased PFS (5-year rates: 38.2% versus 57.2%, adjusted HR 1.47, 95% CI: 1.16–1.87, $P = 0.002$). In another study by the same author [25], sarcoma dominance was associated with decreased PFS and cause-specific survival in homologous cases (both, $P < 0.05$) but not in heterologous cases. In the present study, neither LVI nor histologic subtype had an impact on survival outcomes, which may have been influenced by the missing data.

The role of isolated radiotherapy is not yet clear in the adjuvant setting for patients with UC. A large study conducted by Callister *et al.* [26] retrospectively evaluated 300 patients with clinical stage I–III UC (53% was treated with adjuvant surgery and radiotherapy). The addition of radiotherapy resulted in an absolute 20% reduction in the risk of pelvic recurrence as compared with surgery alone (28% versus 48%, respectively, $P = 0.0002$), however there was no impact on five-year OS (27% versus 36%, $P = 0.10$). In a randomized clinical trial, carried out by the European Organization for Research and Treatment of Cancer-Gynecological Cancer Group (EORTC-GCG), to assess the efficacy of adjuvant radiotherapy alone in patients with endometrial sarcoma, 91 patients with UC were included. Judging by the initial analysis of the general population there was a reduction in local relapse (14% versus 24%, $P = 0.004$) but there was no effect on either PFS or OS [27]. Extrapolating data from studies related to the treatment of high-risk endometrial adenocarcinoma, some experts have suggested to offer adjuvant EBRT or vaginal brachytherapy to reduce the risk of a local recurrence, mostly depending on nodal status and a properly performed lymphadenectomy. The data for the use of radiotherapy after adjuvant chemotherapy is controversial and still requires further investigation [28, 29].

The benefit of adjuvant chemotherapy over WAI was shown with the regimen CIM in the GOG 150 trial. Although not statistically significant, the risk of recurrence and estimated death in the chemotherapy arm were 21% lower (HR 0.79, 95% CI: 0.53–1.18) and 29% lower (HR 0.71, 95% CI:

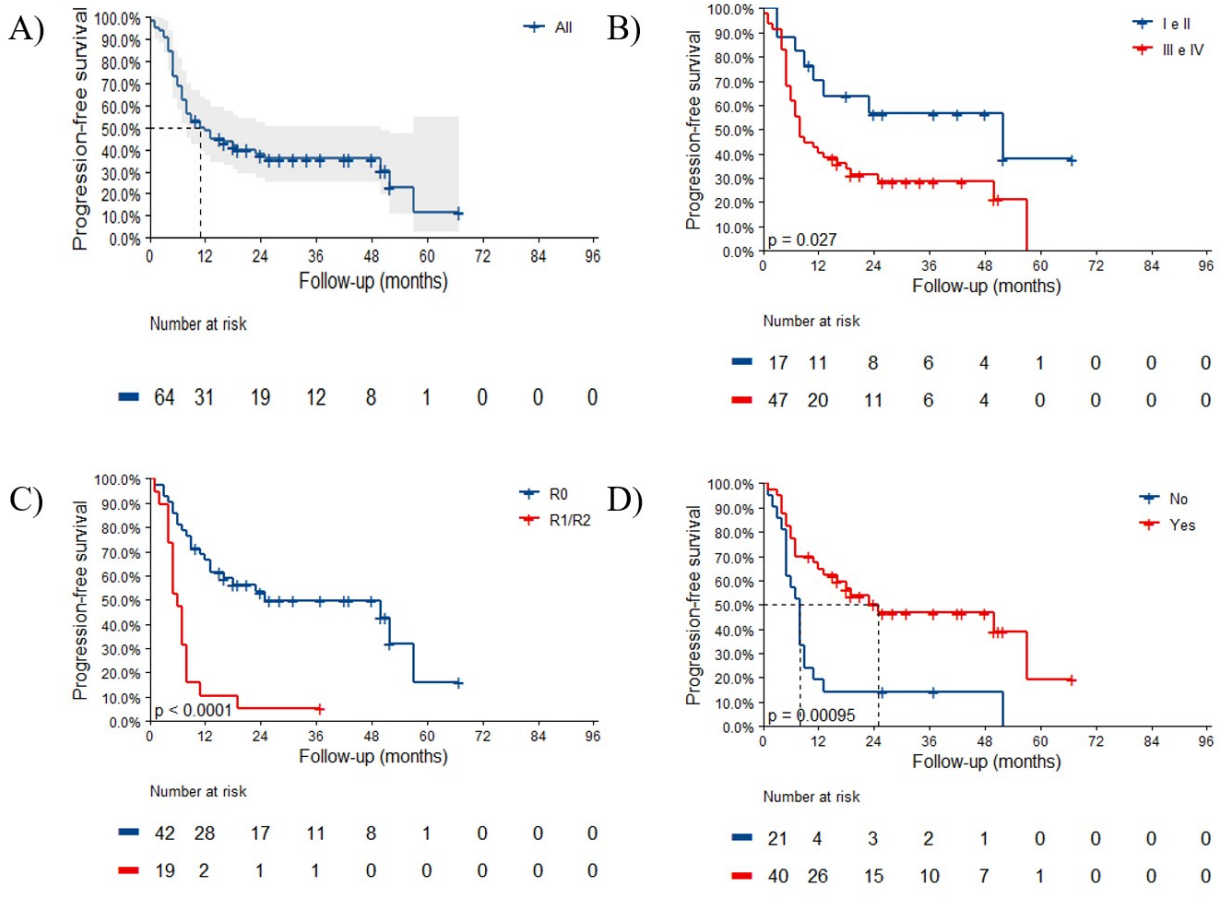


**Fig. 1. Progression-free survival by: (A) Overall population, (B) Staging, (C) Residual disease, and (D) Lymphadenectomy**. The tick marks indicate censored data.

0.48–1.04) when compared to WAI [13]. Thereafter, combined chemotherapy regimen has become the standard of care for both adjuvant and palliative treatment based on results from a meta-analysis published in 2013, where women undergoing doublet chemotherapy had a significantly lower risk of death and disease progression than women who received single-agent ifosfamide (HR 0.75, 95% CI: 0.60–0.94 and HR 0.72, 95% CI: 0.58–0.90 for OS and PFS, respectively) [14].

However, in both adjuvant and palliative settings, the best chemotherapy regimen for gynecological carcinosarcoma has not yet been established. The first phase III study to assess the doublet regimen for gynecological carcinosarcoma was performed by the GOG and included patients with advanced, persistent, or recurrent disease. Patients were randomized to ifosfamide with or without cisplatin. The doublet showed a significantly higher ORR and better median PFS, with no benefit in terms of OS [30]. Based on phase II studies, which showed activity of paclitaxel in gynecological carcinosarcomas [17, 30], the next phase III trial compared ifosfamide with or without paclitaxel in a similar population of advanced disease. And for the first time, a doublet showed a significant gain in OS (13.5 versus 8.4 months, $P = 0.03$), PFS (3.6 versus 2.0 months, $P = 0.03$), as well as RR (45% versus 29%, $P = 0.01$) [31].

Importantly, the median PFS and OS in the current cohort were similar to those of women randomized to the CP arm of the recently presented GOG 261 trial. In this study, CP was compared for noninferiority with PI in more than 600 women with newly diagnosed stage I to IV gynecological carcinosarcoma. CP was non-inferior to PI for median OS (37 versus 29 months; HR 0.87; 90% CI: 0.70–1.075) and had a higher median PFS (16 versus 12 months; HR 0.73; $P \leq 0.01$ for NI, $P < 0.01$ for superiority) [16].

The toxicity profile of the CP regimen in the present study was similar to that of previous clinical trials in patients with carcinosarcoma and other gynecological tumors [32]. Mild myelotoxicity was quite common, but few episodes of febrile neutropenia occurred. Manageable gastrointestinal adverse effects were also observed but without major consequences or treatment interruptions. Peripheral neuropathy has also been widely reported as an adverse effect of paclitaxel.

Even though this is a study performed by one single institution, it has several positive aspects. Carcinosarcoma is a rare gynecological tumor, having included 64 patients in the analysis it can be considered a success when compared to the sample size of other smaller series that also evaluated

**Table 4. Univariate and multivariate analysis according to survival outcomes.**

| | Crude HR for PFS (CI 95%, *P*-value) | Adjusted HR for PFS (CI 95%, *P*-value) |
|---|---|---|
| **Age** | **1.04 (1.01–1.08, *P* = 0.026)** | 1.03 (0.99–1.07, *P* = 0.158) |
| BMI | 1.02 (0.97–1.06, *P* = 0.503) | |
| LVI | | |
| Yes* | | |
| No | 0.66 (0.19–2.29, *P* = 0.508) | |
| Histological subtype | | |
| Heterologous* | | |
| Homologous | 0.56 (0.23–1.39, *P* = 0.210) | |
| **Staging** | | |
| **I–II*** | | |
| **III–IV** | **2.37 (1.09–5.17, *P* = 0.030)** | 1.67 (0.69–4.05, *P* = 0.257) |
| **Omentectomy** | | |
| **No*** | | |
| **Yes** | **0.58 (0.3–1.09, *P* = 0.093)** | 1.01 (0.48–2.09, *P* = 0.987) |
| **Surgical margin status** | | |
| **Optimal surgery (R0) *** | | |
| **Suboptimal surgery (R1–R2)** | **4.48 (2.29–8.77, *P* < 0.001)** | 3.09 (1.29–7.45, *P* = 0.011) |
| Lymphadenectomy | | |
| No* | | |
| Yes | 0.35 (0.19–0.67, *P* = 0.001) | |
| | Crude HR for OS (CI 95%, *P*-value) | Adjusted HR for OS (CI 95%, *P*-value) |
| **Age** | **1.04 (1.00–1.08, *P* = 0.043)** | 1.01 (0.94–1.07, *P* = 0.860) |
| BMI | 1.01 (0.96–1.06, *P* = 0.834) | |
| LVI | | |
| Yes* | | |
| No | 0.54 (0.12–2.45, *P* = 0.425) | |
| **Histological subtype** | | |
| **Heterologous*** | | |
| **Homologous** | **0.49 (0.18–1.32, *P* = 0.159)** | 0.58 (0.21–1.61, *P* = 0.292) |
| **Staging** | | |
| **I–II*** | | |
| **III–IV** | **2.64 (1.09–6.43, *P* = 0.032)** | 1.45 (0.46–4.56, *P* = 0.520) |
| Omentectomy | | |
| No* | | |
| Yes | 0.56 (0.28–1.11, *P* = 0.097) | |
| **Surgical margin status** | | |
| **Optimal surgery (R0) *** | | |
| **Suboptimal surgery (R1–R2)** | **4.36 (2.17–8.75, *P* < 0.001)** | 3.30 (1.21–9.01, *P* = 0.019) |
| Lymphadenectomy | | |
| No* | | |
| Yes | 0.27 (0.14–0.52, *P* < 0.001) | |

*Reference.

The variables of the final model selected for analysis by the Cox multiple model were highlighted in bold.

BMI, Body mass index; HR, Hazard ratio; LVI, Lymphovascular invasion; OS, Overall survival; PFS, Progression-free survival; R0, no cancer cells seen microscopically at the primary tumor site; R1, cancer cells present microscopically at the primary tumor site; R2, macroscopic residual tumor at primary cancer site or regional lymph nodes.

the use of the CP regimen in this subset. A central pathology review was performed to confirm the diagnosis of gynecological carcinosarcoma and for the analysis of clinicopathological factors. The study population is homogenous since the same surgery team performed all of the surgeries. Lastly, a thorough descriptive presentation of clinicopathological variables was performed here.

However, there are several limitations to be highlighted. The retrospective nature, missing data, nonstandard records in the database, and the small sample size can keep analyzes vulnerable to confounding factors. The lack of a QoL questionnaire did not allow for monitoring the impact of CP use on the patients' quality of life.

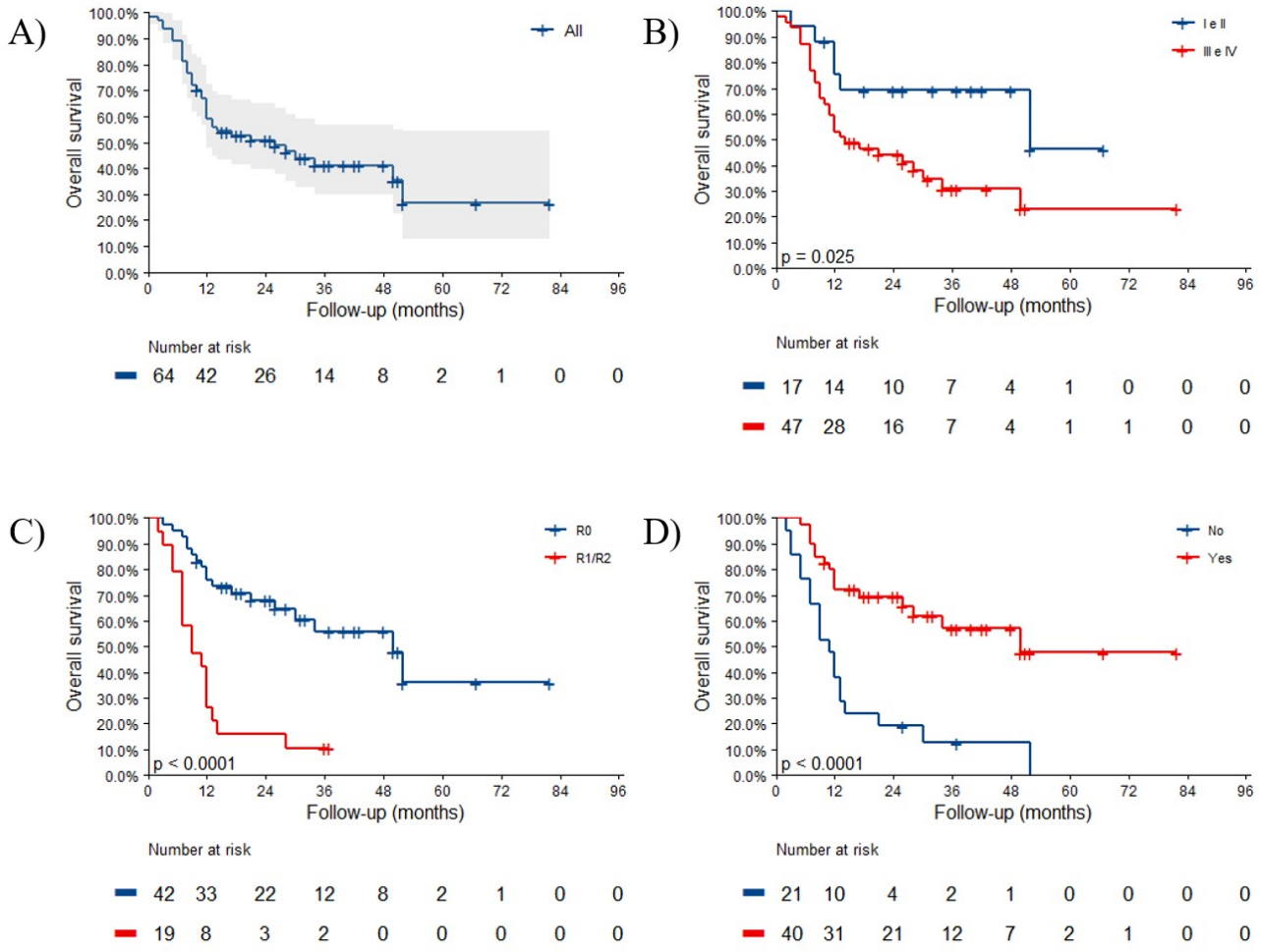


**Fig. 2. Overall survival by: (A) Overall population, (B) Staging, (C) Residual disease, and (D) Lymphadenectomy**. The tick marks indicate censored data.

Although CP is likely to be the most appropriate chemotherapeutic schedule with a better cost-effective profile, the survival outcomes in patients with gynecological carcinosarcoma remain poor and recurrence is extremely common. The need for more effective therapies is urgently required. A better understanding of possible prognostic and predictive biomarkers, such as; histologic subtype (heterologous versus homologous), tumor heterogeneity and molecular aberrations, such as *p53, MSH2, MSH6, PTEN, PI3KCA* and *ARID1A,* are required to better select patients for new approaches [33, 34].

Unlike other epithelial gynecological tumors, studies assessing new targeted therapies in gynecological carcinosarcoma are very scarce and with disappointing results [35]. Some data suggest that PD-L1, as well as PD-L2 and CD8+, is highly expressed by most carcinosarcomas, predominantly in epithelial components [36, 37]. Immunotherapy should be evaluated in prospective trials for the treatment of gynecological carcinosarcomas and further studies are needed to better select patients who are better suited to respond to these therapies. Finally, a recent study with gynecological carcinosarcoma showed similarities of HER-2 expression/amplification profiles to endometrial serous carcinomas. Therefore, HER-2 is likely to be a potential therapeutic target in this subset [38].

## 5. Conclusions

The current cohort respectfully corroborates with data from previous series suggesting that, with manageable mild toxicities, CP is posed to be an effective option for the treatment of gynecological carcinosarcoma. Further prospective studies comparing different cytotoxic chemotherapy regimens, whilst also evaluating the association of new molecular target therapy agents and immunotherapy, is the best way to set the standard of care. The study of molecular biomarkers may provide more answers about their role in predicting response to therapeutic agents as well as prognosis.

## Author contributions

The study design was planned by JLS and ACM; LZA, ALG, BRLA, DSBR, TCF, JLS and ACM were involved in the data collection in medical records; JLS, EP and ACM

participated in the analysis and interpretation of the data. All authors (JLS, LZA, ALG, BRLA, DSBR, TCF, EP and ACM) contributed to the writing, critical reviewing and submission of the manuscript. All authors approved this final manuscript.

## Ethics approval and consent to participate

The study was approved by the Ethics in Human Research Committee of INCA, Rio de Janeiro, Brazil, under registration number 03727818.2.0000.5274, and conducted following Good Clinical Practice guidelines. For this type of study with an observational retrospective design, informed consent was not required.


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## Conflict of interest

The authors declare no conflict of interest.

## Data availability

The data that support the findings of this study are available from the corresponding author but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data however may be available from the authors upon reasonable request and after a review of the Institutional Review Board.

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