PROGRESOS DE
Obstetricia y Ginecología
Revista Oficial de la Sociedad Española de Ginecología y Obstetricia

Prog Obstet Ginecol 2019;62(2):130-135

Trabajo Original

Prognosis and treatment-selection criteria for patients with high-grade stage IIIc-IV serous ovarian, fallopian tube or peritoneal cancer

Pronóstico y selección de tratamiento en pacientes con cáncer seroso de ovario, de trompas de Falopio o peritoneal de alto grado, estadio IIIc-IV

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Abstract

Objective: To determine the impact of implementing strict treatment-selection criteria on the overall outcome of women with high-grade serous advanced stage ovarian, fallopian tube, or primary peritoneal carcinoma.

Material and methods: We included patients treated for high-grade serous advanced stage ovarian, fallopian tube, or primary peritoneal carcinoma at our Institution from January 2007 to March 2015. All other non-serous, low-grade histology tumors and secondary cytoreductions were excluded. strict treatment-selection criteria was used to decide on primary cytoreductive surgery versus neoadjuvant chemotherapy and type of adjuvant therapy. Collected data included patient and tumor characteristics, preoperative diagnostic procedures, surgical treatment, perioperative complications, and neoadjuvant and adjuvant chemotherapies. Appropriate statistical tests were used and survival analysis performed.

Results: We identified 71 eligible patients. Mean age was 58.5 ± 11.8 years, 28.2% received neoadjuvant chemotherapy, and 77.5% had optimal cytoreductive surgery to < 1 cm residual disease. Major complications were observed in 16.9% of women, with no significant difference between neoadjuvant chemotherapy and primary cytoreductive surgery groups. With a median follow-up of 35.7 months, median overall survival was not achieved and 57.2% of patients were alive 54 months after surgery. A total of 24 out of 71 (33.8%) died of disease, 11 (45.8%) within two years after surgery. Median progression-free survival was 19.5 months (95% CI 14.8-24.3).

Conclusions: Applying strict treatment-selection criteria for patients with high-grade serous advanced stage ovarian, fallopian tube, or primary peritoneal carcinoma ensures few surgical complications and excellent survival rates for the majority of these women.

Key words:

Disease-free survival. Ovarian cancer. Patient selection. Survival analysis. Treatment outcome.

Resumen

Objetivo: determinar el impacto de la implementación de criterios estrictos de selección de tratamiento sobre el pronóstico de las mujeres con carcinoma seroso de ovario, trompa de Falopio o peritoneal primario en estadio avanzado y de alto grado.

Material y métodos: entre enero de 2007 y marzo de 2015 se incluyeron pacientes tratadas por carcinoma ovárico seroso avanzado de alto grado, trompa de Falopio o carcinoma peritoneal primario en nuestro hospital. Se utilizaron criterios estrictos de selección de tratamiento para decidir sobre la cirugía citorreductora primaria versus quimioterapia neoadyuvante y el tipo de tratamiento adyuvante. Los datos recogidos incluyeron características del paciente y del tumor, procedimientos diagnósticos preoperatorios, tratamiento quirúrgico, complicaciones perioperatorias y quimioterapias neoadyuvantes y adyuvantes. Se utilizaron pruebas estadísticas adecuadas y se realizó un análisis de supervivencia.

Resultados: se incluyeron 71 pacientes. La edad media fue de 58,5 ± 11,8 años, el 28,2% recibió quimioterapia neoadyuvante y el 77,5% tuvo una cirugía citorreductora óptima (< 1 cm de enfermedad residual). Se observaron complicaciones mayores en el 16,9% de las mujeres, sin diferencias significativas entre los grupos de quimioterapia neoadyuvante y de cirugía citorreductora primaria. Con una mediana de seguimiento de 35,7 meses, no se alcanzó la mediana de supervivencia global y el 57,2% de los pacientes estaban vivas 54 meses después de la cirugía. Un total de 24 de 71 (33.8%) murieron de enfermedad, 11 (45.8%) en los dos años después de la cirugía. La mediana de supervivencia libre de progresión fue de 19,5 meses (IC del 95%: 14,8-24,3).

Conclusiones: la aplicación de criterios estrictos de selección de tratamiento para pacientes con carcinoma seroso ovárico, de trompa de Falopio o carcinoma peritoneal primario en estadio avanzado de alto grado asegura pocas complicaciones quirúrgicas y buenas tasas de supervivencia para la mayoría de estas pacientes.

Palabras clave:

Supervivencia libre de enfermedad. Cáncer de ovario. Selección de pacientes. Análisis de supervivencia. Resultados del tratamiento.

Recibido: 18/02/2019
Aceptado: 26/02/2019

Sainz de la Cuesta R, González-Cortijo L, Jiménez de la Peña M, Murillo R, Hernández G, Iacoponi S, et al. Prognosis and treatment-selection criteria for patients with high-grade stage IIIc-IV serous ovarian, fallopian tube or peritoneal cancer. Prog Obstet Ginecol 2019;62(2):130-135. DOI: 10.20960/j.pog.00180.

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INTRODUCTION

Epithelial ovarian cancer is the most lethal gynecologic malignancy in the developed world. Approximately 200,000 women worldwide are diagnosed with ovarian cancer each year and 125,000 (62.5%) die from this disease (1). In addition, this neoplasm represents a heterogeneous group of tumors, which are classified according to cell subtypes including high-grade, low-grade serous, clear cell, endometrioid, and mucinous (2). Each histological type represents a unique disease, with different immunophenotypes, gene profiling and response to chemotherapy (3). These facts make ovarian cancer treatment a challenge. For the purpose of this study we decided to include only high-grade serous ovarian, fallopian tube, and peritoneal carcinomas, which represent approximately 70% of malignant epithelial ovarian tumors and share many morphologic, molecular and chemo-response similarities (4-6).

Primary cytoreductive surgery (PCS) followed by platinum-based chemotherapy has been the standard of care for women with advanced stage ovarian cancer since 1978 (7). Recently, neoadyuvant chemotherapy (NAC) has gained in popularity, based on two randomized trials, where similar overall survival (OS) and decreased surgical complications were observed among women treated with NAC compared to PCS (8, 9). These findings contrast with other observational studies and meta-analyses, which demonstrate that women with complete tumor resection to no visible residual disease after surgery have the best survival, when compared to NAC (10-13). Given the available data, the question as to whether to start with NAC or with PCS remains. In addition, intraperitoneal chemotherapy (IP) has shown a clear survival benefit over traditional intravenous (IV) therapy in low volume, advanced stage disease, following PCS (14-16). Despite this information, IP therapy has not been widely adopted because it adds complexity, toxicity and cost in comparison with the traditional delivery method. The combination of systemic and antiangiogenic targeted therapy (Bevacizumab) has also been shown to enhance survival in patients with gross residual disease following debulking surgery (17-19).

The purpose of this study is to provide clinicians treating ovarian, fallopian tube, and peritoneal cancer patients our selection criteria for high-grade serous, advanced stage disease and report surgical complications and survival.

MATERIAL AND METHODS

Informed consent was obtained from all individual participants included in the study. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The authors received no funding for this work and declare that there are no conflicts of interest.

PATIENTS AND DEFINITIONS

The study criteria included patients with a biopsy-proven diagnosis of high-grade serous advanced stage ovarian, fallopian tube, or primary peritoneal carcinoma (HGSASC) who underwent cytoreductive surgery between January 2007 and March 2015 at our institution. All surgical interventions were carried out by the same American Board Certified gynecologic oncologist. Patients with follow-up shorter than 24 months after surgery were excluded.

Clinical and disease characteristics, including age and serum cancer antigen 125 (CA-125) at diagnosis, tumor stage (2), surgical procedure, residual disease after primary surgery, postoperative complications, postoperative blood transfusion, chemotherapy, recurrence history, date of last follow-up, and patient status at the end of follow-up (with disease, disease-free, or death) were collected from electronic chart review.

Cytoreductive surgery was considered optimal if residual disease was ≤1 cm, and sub-optimal if residual tumor was >1 cm at the end of the surgical procedure (20). Surgery was classified as standard or radical following Pomel and Dauplat model (21). We defined major postoperative complications according to Erekson et al. criteria (22), including intestinal morbidity (perforation or fistula) as a major complication. Blood transfusion within the first 72 hours after surgery, if not associated with a reoperation, was not considered a major complication. We defined overall survival (OS) as the time from the date of surgery until death. Survival data was censored to the date patients were last known to be alive. We defined progression-free survival (PFS) as the time from the date of surgery to date of first recurrence. Women who did not relapse or die were censored at the date of their last follow-up visit.

Treatment-selection criteria

All patients were presented at our weekly Gynecologic Tumor Board Meeting. An agreed joint decision was made among Gynecologic and Medical Oncologists, Gynecologic Pathologists, and Radiologists as to whether the patients were candidates for PCS or NAC. This decision was based on the following diagnostic and treatment criteria:

A favorable pelvic examination performed by the Gynecologic Oncologist responsible for the surgical procedure.

Serum tumor markers: CA-125, CA 19-9 and carcinoembryonic antigen (CEA) were obtained. In cases with a significant elevation of the CA 19-9 or CEA compared to the CA-125, a gastroscopy and colonoscopy were performed to rule out non-gynecologic cancer.

A diffusion-weighted magnetic resonance imaging (DWMRI) of the abdomen and pelvis, read by the same radiologist, expert in gynecologic malignancies. Women with extra-abdominal diseases, parenchymal liver or supra-renal node metastasis, or small bowel mesenteric-root involvement, were deemed inoperable and assigned to NAC. In addition, we applied a score system using MRI and DW, previously described by our group (23). We established that a score of ≥ 6 had a high predictive value for sub-optimal cytoreductive surgery (SOCS). These patients were not considered candidates for primary surgery and were also allocated to NAC. The remaining women had a PSC performed.

Patients assigned to NAC received three cycles of intravenous (IV) Paclitaxel and Carboplatin every 21 days, followed by interval cytoreductive surgery and three more cycles of postoperative chemotherapy.

Women with optimal cytoreductive surgery (OCS) and ≤ two intestinal resections had an intraperitoneal (IP) catheter placed intraoperatively and received IP chemotherapy (IV paclitaxel 135 mg/m2 day 1; IP cisplatin 75 mg /m2 day 2; and IP paclitaxel 60 mg / m2 day 8). For institutional reasons, IP therapy did not begin until September 2010.

Women with OCS and more than two bowel anastomoses, and women with SOCS received IV adjuvant chemotherapy (paclitaxel 175 mg/m2 and carboplatin AUC 5-6 every 21 days). Bevacizumab 15 mg/kg was added to treatment from 2011 onwards. Antiangiogenic target therapy was started after two cycles if an intestinal resection was performed.

Statistical analysis

Frequency counts and percentages were used to describe categorical variables; mean ± standard deviation or median and interquartile range (IQR) range were used for continuous variables depending on the data distribution. To compare categorical variables, we used chi-square test (or Fisher exact test when needed). Overall and progression-free survival rates and survival medians were calculated using life tables and the Kaplan-Meier method. The log-rank test was used to investigate the difference in overall and disease-free survival between the studied groups. Differences were considered significant at a level of $p < 0.05$. We used the IBM SPSS statistical software program, version 21.0 (IBM, Armonk, New York, USA).

RESULTS

Between January 2007 and March 2015, a total of 139 consecutive surgical procedures were performed at HUQSM for patients with the diagnostic suspicion of ovarian, fallopian tube, or peritoneal cancer. Excluding secondary cytoreductions and other histological types, 74 corresponded to biopsy-proven high-grade serous advanced stage ovarian, fallopian tube, or primary peritoneal carcinoma (HGSASC). Three patients did not achieve the minimum follow-up of 24 months and were excluded from the final analyses.

Demographic and clinical characteristics of the study group are shown in Table I. A total of 19 major postoperative complications occurred in 12 patients (16.9%). These adverse events were: mortality (1 patient); vascular morbidity (5 patients); wound morbidity (3 patients); infectious morbidity (4 patients); renal morbidity (1 patient); and intestinal morbidity (5 patients).

Patients with stage IV disease (16 patients) were more frequently selected for NAC (8/20, 40%), as compared with PCS (8/51, 15.7%) (p= 0.05); this was close but not statistically significant. We did observe a significant difference in the rate of radical surgery performed in the PCS cohort (n=32/51, 62.7%), as compared with the NAC (n=5/20, 25%) (p=0.007). However, no significant difference (p=0.2) for major complications was observed between the two groups [NAC (1/20; 5%) vs PSC (11/51; 21.6%)]. In addition, there was no difference in the rate of optimal surgery (p = 0.76) performed in either group [NAC (n= 15/20, 75%) vs PCS (n= 40/51, 72.7%)].

After a median follow-up of 35.7 months (IQR: 25.8-53.7), 47 patients (66.2%) were alive and 21 (29.6%) were disease-free. The estimated median progression-free survival was 19.5 months (95% CI: 14.8-24.3) (Figure 1). Three patients with primary peritoneal cancer recurred within six months of surgery. A total of 58 patients (81.7%) remained disease-free 12 months after surgery and 31 (43.7%) were disease-free 24 months after the procedure. No statistically significant difference was observed (p=0.25) in median progression-free survival between patients who underwent NAC (19.2 months; 95% CI: 12.9-25.4) as compared with PCS (19.5 months; 95% CI: 13.6-25.4).

At the end of the study period (median follow-up: 35.7 months), 24 patients (33.8%) died and 11 deaths (45.8%) occurred within 24 months of surgery, with a survival range of 15 days–118 months (9.8 years). After the minimum follow-up of 24 months, 60 patients (84.5%) were still alive. At 36 months (3 years), the cumulative probability of surviving was 69.9%. At 54 months (4.5 years), this probability of being alive was 57.2%. (Figure 2). All patients with a follow-up longer than 54 months were alive and free of disease and therefore, the median overall survival was not achieved. The estimated mean OS was 80.2 months (95% CI: 68.3- 92.2). We found no significant difference (p=0.2) in the mean overall survival between patients who underwent NAC (53.7 months; 95% CI: 39.4-68) and patients undergoing PCS (84.6 months; 95% CI: 70.7-98.6).

Table I
Demographic and clinical characteristics

	N=71
Age at diagnosis (mean ± SD)	58.5 ± 11.8
FIGO stage†	
IIIC	55 (77.5%)
IV	16 (22.5%)
Origin	
Ovary	49 (69%)
Fallopian tube	16 (22.5%)
Peritoneal	6 (8.5%)
Serum CA-125 U/ml at diagnosis. Median (IQR)	345 (IQR: 92-907.5)
Neoadjuvant chemotherapy	
No	51 (71.8%)
Yes	20 (28.2%)
Optimal surgery	
No	16 (22.5%)
Yes	55 (77.5%)
Radical surgery	
No	34 (47.9%)
Yes	37 (52.1%)
Lymphadenectomy	43 (60.2%)
Para-aortic lymphadenectomy	41 (57.7%)
Pelvic lymphadenectomy	38 (53.5%)
Bowel resection	21 (29.6%)
Splenectomy	26 (36.6%)
Hepatic resection	1 (1.4%)
Colostomy	3 (4.2%)
Major postoperative complications	
No	59 (83.1%)
Yes	12 (16.9%)
Postoperative blood transfusion	
No	51 (71.8%)
Yes	20 (28.2%)
IV adjuvant chemotherapy	43 (60.6%)
Intraperitoneal chemotherapy	13 (18.3%)
IV adjuvant therapy and Bevacizumab	15 (21.1%)
Treatment outcome	
Recurrence	53 (74.6%)
With disease at the end of follow-up	26 (36.6%)
Disease-free at the end of follow-up	21 (29.6%)
Death	24 (33.8%)

†FIGO, International Federation of Gynecology and Obstetrics (2)

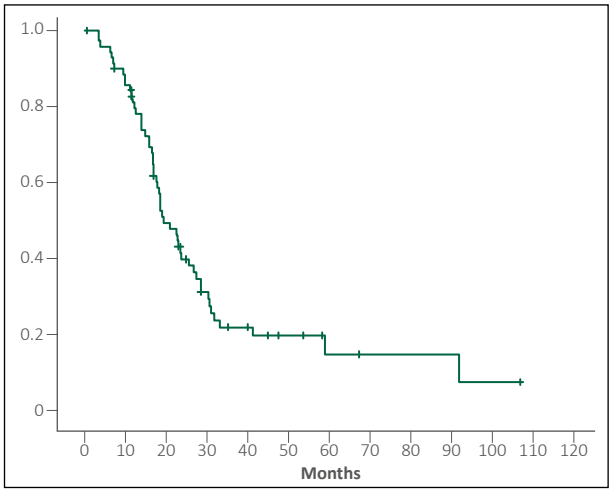

Figure 1. Kaplan-Meier curve for progression-free survival.

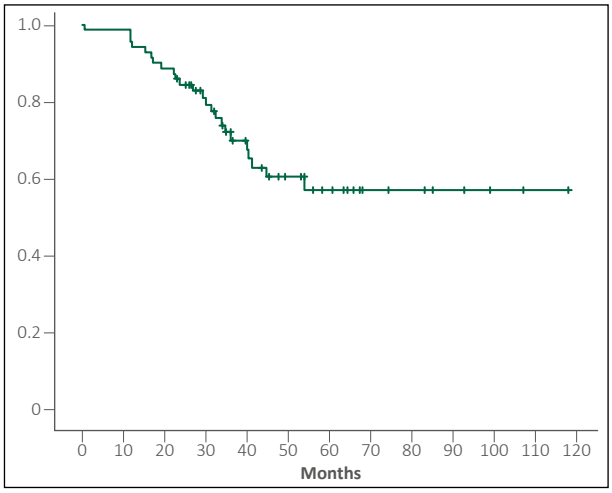

Figure 2. Kaplan-Meier curve for overall survival.

DISCUSSION

We believe that the main objective in managing patients with HGSASC is to achieve complete tumor cytoreduction (R0=no residual tumor cells) when completing primary cytoreductions (including surgery and chemotherapy). To reach this goal, we established STSC when deciding how to treat women with high volume, highly chemo-sensitive carcinoma. The ultimate purpose is to improve the OS without major surgical complications. In this series, we observed that 66% or our patients were alive 54 months from diagnosis with a 17% rate of major complications. Survival outcomes in the EORTC (8) and CHORUS (9) trials were much lower, reporting an OS of 24 and 30 months, respectively. Our estimated mean OS was 80 months, not achieving median OS due to the high survival rate of our patients. In addition, the complication rate in the CHORUS

trial (9) was 3% higher. We believe this difference in survival and complication rates may be a result of our strict patient selection and treatment protocol. We consider it important that we only included high-grade serous histology and selected the appropriate patients for PSC. These facts, added to the low number of patients, may explain why we did not find survival differences among PSC vs NAC. It is worth highlighting that 50% of our patients with primary peritoneal cancer were platinum-resistant, indicating, as previously described by other authors (4), that peritoneal and ovarian cancers may be linked to different carcinogenic pathways and should probably be treated differently.

Our first criterion states that each patient should undergo a thorough review of symptoms and a physical evaluation (including pelvic bimanual and rectovaginal examinations) by an experienced gynecologic oncologist, designed to determine anatomic location and size of the ovarian neoplasm, as well as possible sites of metastasis. This evaluation allows identification of loco-regional disease extension for surgical approach strategy, and recognition of poor candidates for aggressive surgical procedures.

The differential diagnosis of peritoneal carcinomatosis includes metastatic disease from other primary sites. Therefore, we consider it important to obtain preoperative serum tumor markers, as these may suggest other histologies that could change both medical and surgical approaches. Baseline markers are also important for monitoring response to therapy (24). Gastrointestinal tumors may elevate both CEA and CA-19.9. In these cases, preoperative endoscopies should be performed to rule out stomach or colon cancers. Systematically we send intraoperative tumor biopsy for pathology confirmation, as this may change our surgical management. Well differentiated serous and endometroid tumors, as well as mucinous, clear cell or transitional cell carcinomas are much less chemo-sensitive, for which, under our perspective, a more aggressive surgical procedure would be indicated (3). In such cases, an intraperitoneal catheter would not be inserted, as this type of adjuvant chemotherapy would not be our first choice.

Probably the most important and difficult criterion to meet is the preoperative identification of patients at highest risk for suboptimal debulking surgery. When identified, these patients are treated with NAC instead of primary cytoreduction, based on EORTC (8) and CHORUS trials (9). Using a predictive score of DWMRI ≥ 6, we previously reported (23) 91% accuracy (75% sensitivity and 98% specificity) as compared with exploratory laparotomy. In this study, we performed optimal cytoreductive surgery in approximately 80% of the patients, reconfirming the precision of this tool at our Institution. Other authors have used different techniques in order to predict optimal surgery, including Computed Tomography (CT) of abdomen and pelvis (25), CA-125 and ascites volume (26), or diagnostic laparoscopy (27-29) with conflicting results (34-77% accuracies). At present, and to our knowledge, there are no validated tools to predict the likelihood of optimal cytoreduction. We recommend that individual institutions always use the same method, based on their available techniques, resources and experience, in order to maximize surgical debulking feasibility.

Several IP therapy trials (14-16) have demonstrated a survival benefit for patients with small volume residual diseases (< 1 cm). Despite these studies, IP chemotherapy has not been widely adopted in many centers because it adds complexity and cost to adjuvant therapy (30). Toxicity is another drawback for its application. In our experience, when used in the appropriate patient and dosage (we lower cisplatin to 75 mg/m^2 on day 2 of chemotherapy regimen), toxicity was not a concern. Women with multiple intestinal anastomosis, or suboptimal cytoreduction were not considered candidates for IP therapy. Only 18% of our patients had an IP catheter inserted during surgery. This low number, given that optimally debulked patients represented 78% of the total, is a consequence of not only our strict selection protocol, but also the fact that IP therapy was implemented later in our institution. Eight patients received at least four cycles, with six undergoing this type of therapy throughout the treatment. Abdominal pain was the main reason for withdrawal.

Randomized control trials conducted by both Gynecologic Oncology Groups (GOG 0218) and International Cooperative Group for Ovarian Neoplasms (ICON-7) (31, 32) showed a significant prolonged PFS in patients with residual diseases > 1 cm treated with bevacizumab + chemotherapy, as compared with chemotherapy alone (an improvement of 3.8 months in the GOG study and 5.4 months in the ICON trial). Based on this data, we decided to treat our sub-optimally cytoreduced patients with carboplatin + paclitaxel + bevacizumab (15 mg/kg) every 3 weeks for 6 cycles, followed by 12 cycles of maintenance therapy with bevacizumab (32). Fifteen of our patients received this combination. Women with a bowel resection did not start antiangiogenic therapy until the second or third cycle of therapy. We saw no major GI complications in this series. IP chemotherapy following optimal debulking after NAC and interval surgery may also be an option worth considering. Further studies are needed to support its use in our daily practice.

This study has the limitations intrinsic to handling observational data and those of possible selection and collection bias due to non-randomized allocations. However, we believe it is the first investigation to study survival and surgical complications in a very homogeneous group of patients with HGSASC managed by the same multidisciplinary team (surgeon, medical oncologist, radiologist and pathologist).

CONCLUSIONS

The key to improving survival with minimal surgical complications rates, in patients with high-grade serous advanced stage ovarian, fallopian tube, or primary peritoneal carcinoma, is to establish a strict treatment-selection criteria protocol, based on the experience and technical capabilities of each multidisciplinary team. Individualized protocols should be adopted.

ACKNOWLEDGMENT

We wish to thank Peter Bonney for his support in proofreading this article.

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