

# 2018 in review: gynecologic cancer insights

2018 em revisão: insights sobre câncer ginecológico

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## ABSTRACT

Gynecologic cancers constitute an important burden of disease around the world. Estimates from GLOBOCAN 2018 reveals approximately 1,247,300 incident cases and 596,000 related deaths of cancers of the uterine cervix, corpus uteri, and ovarian, annually around the world. In 2018 lots of promising results to improve disease control have been presented at international gynecological cancer meetings. The current review highlights some of the top gynecologic cancer news of 2018, including the new standard of care for BRCA mutant ovarian cancer patients with maintenance olaparib in first line, benefit of bevacizumab rechallenge for relapsed ovarian cancer patients, and the unexpected results of worse overall survival with minimally invasive surgery in early cervical cancer, among others.

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## RESUMO

Os tumores ginecológicos constituem um verdadeiro fardo à saúde feminina mundialmente. Estimativas do GLOBOCAN 2018 demonstram cerca de 1.247.300 casos e 596.000 mortes anualmente relacionadas aos tumores ginecológicos. Em 2018 foram apresentados trabalhos importantes sobre o manejo destes tumores nos principais congressos internacionais. Esse artigo de revisão destaca alguns destes trabalhos como a manutenção de olaparibe em primeira linha para as pacientes com câncer de ovário e mutação de *BRCA*, o benefício da re-exposição ao bevacizumabe para pacientes com câncer de ovário recidivado (platino sensível), os resultados inesperados da cirurgia minimamente invasiva em câncer de colo uterino inicial, dentre outros.

**Descritores:** Neoplasias Genitais Femininas. Revisão.

## INTRODUCTION

Gynecological oncology was the focus of great advances in 2018. Some standards of care have been affected, such as in ovarian and cervical cancer. In cervical cancer, the awaited LACC trial has been presented, and its unexpected results raises questions on the safety of minimally invasive surgery (MIS). In ovarian cancer, SOLO1 trial recasts treatment for *BRCA* pathogenic variant carriers, MITO-MANGO shows benefit of bevacizumab rechallenge for relapsed patients and, GOG 213, on the opposite way of DESKTOP III trial, brings uncertainty on the role of secondary surgery. This year's review is a snapshot of the year, condensing selected gynecologic cancer trials that can affect clinical practice (Table 1).

### CERVICAL CANCER: A NEW ERA AFTER THE LACC TRIAL

LACC trial, the first randomized controlled trial comparing MIS, laparoscopy or robotic, versus open surgery for patients with initial cervical cancer have been just published. The unexpected results immediately alerted the oncology community as nobody was expecting that MIS would have worse disease free survival (DFS) and overall survival (OS)<sup>(1)</sup>.

Patients included should have FIGO stage IA1 (lymphovascular invasion) to IB1, squamous cell, adenocarcinoma or adenosquamous histology; 312 patients had been randomized to open radical hysterectomy and 319 patients to MIS (83% laparoscopy and 16% robotic surgery). The majority (92% in both) harbored stage IB1 disease. In the open surgery group, 88% received randomized treatment versus 91% in the minimally invasive surgery group. The conversion rate to laparotomy was 3%. At the time of analysis, information available at 4.5 years was 60%, with over 80% power for the primary endpoint and median follow-up of 2.5 years. The non-inferiority boundary of -7.2% for disease-free survival at 4.5 years was breached (open 97% versus minimally invasive surgery 86%, difference -10.6%, 95%CI -16.4% to -4.7%, difference not significant).

MIS was found to be associated with over a 3-fold increase in disease-free survival (7 of 312 versus 27 of 319, hazard ratio 3.74, 95%CI 1.63–8.58,  $p=0.002$ ). This finding was consistent when adjusted for age, body mass index, stage of disease, lymphovascular space involvement, lymph node involvement, and performance status. MIS was also associated with a decrease in overall survival (3 of 312 versus 19 of 319, hazard ratio 6.00, 95%CI 1.48–20.3,  $p=0.004$ ). Rates of intraoperative complications did not differ by treatment received (11% in both) (Table 1).

Some limitations have to be mentioned about the study: first, the results of open arm were much better than expected, giving the impression that the results from the MIS arm were even worse. Second, the recruitment was suspended after achieving around 90% of the expected number of patients because of the evident worse result of one of the arms (MIS).

In the end, as always, new studies will prove or not these results.

### OVARIAN CANCER: NEW STANDARD OF CARE IN FRONT LINE SETTING AND OTHER OPTIONS IN PLATINUM SENSITIVE RECURRENT DISEASE

#### SOLO1

The phase III study SOLO-1 evaluated the role of olaparib, a PARP inhibitor, as maintenance therapy in patients with newly diagnosed advanced (FIGO III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer with a mutation in *BRCA1*, *BRCA2*, or both. Three hundred and ninety-one patients who had complete or partial response after first-line platinum-based chemotherapy were randomized (2:1) to receive olaparib 300 mg twice daily or placebo for 2 years. Patients who underwent initial or interval surgery (36%) were included, and 18% of them had not achieved complete response after platinum-based treatment. The initiation of maintenance should be between four and eight weeks after the end of chemotherapy.

**Table 1.** Most influential gynecologic cancer trials of 2018

Study	Patients	Design/Objective	Results	HR	P Value
<b>Ovarian</b>					
SOLO1	Newly diagnosed advanced (FIGO III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy	Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. Primary end point was PFS	Significant better rate of freedom from disease progression and from death at 3 years; 60% vs. 27% Data immature for OS	HR: 0.3 (95%CI 0.23 to 0.41)	PFS p value: <0.001
GOG213	Women with recurrent ovarian, peritoneal or fallopian tube cancer and treatment free greater than or equal to 6 months	Determine if secondary cytoreduction in patients with platinum recurrent disease followed by platinum chemotherapy vs platinum chemotherapy would improve survival	Non-significant difference in OS (53.6 vs 65.7 m) neither PFS (18.2 vs 16.5)	HR OS: 1.28 (95%CI 0.92-1.78) HR PFS: 0.88 (95%CI 0.7 - 1.11)	
AGO 2.21	Patients with recurrent platinum sensitive ovarian cancer, front-line bevacizumab allowed	The aim of this trial was to evaluate whether carboplatin/doxil is superior (PFS) to Carboplatin/Gemcitabine when given in combination with bevacizumab	Better PFS for carboplatin/doxil 10 vs 11.5  No difference in OS: 28.2 vs 33.5	PFS HR: 0.75 (95%CI 0.64-0.89)  OS HR: 0.8u3 (95% CI 0.68 - 1.02)	PFS p value: 0.001  OS p value: 0.07
MITO/MANGO	Recurrent platinum sensitive ovarian cancer patients at first relapse who were already treated upfront with bevacizumab	Platinum combo with or without bevacizumab Primary end point was to test with addition of bevacizumab would improve PFS	Better PFS: 8.8 vs 11.8  OS: 27.1 vs 26.6	HR PFS: 0.51 (95%CI 0.41 - 0.65) HR OS: 0.97 (95% I 0.7 - 1.35)	PFS p value: <0.001 OS p value: 0.98
<b>Cervix</b>					
LACC	Patients with stage IA1 (lymphovascular invasion), IA2, or IB1 cervical cancer and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma	Noninferiority of Minimally invasive surgery compared to open surgery based on an expected DFS rate at 4.5 years (noninferiority margin of - 7.2 percentage points for minimally invasive surgery)	DFS at 4.5 years was 86.0% and 96.5% (95% CI, -16.4 to -4.7) 3-year rate DFS, 91.2% vs. 97.1%; 3-year rate OS, 93.8% vs. 99.0%;	HR for disease recurrence or death from cervical cancer, 3.74; 95%CI, 1.63 to 8.58 HR for death from any cause, 6.00; 95%CI, 1.77 to 20.30	DFS p value: 0.87 for non-inferiority
<b>Endometrial</b>					
Portec 2	High-intermediate risk endometrial cancer (>60 years with either a grade 3 or > 50% myometrium invasion)	Radiotherapy alone or brachytherapy Primary endpoints was vaginal recurrence	10-year vaginal recurrence (VR) was 3.4% versus 2.4% for VBT vs. EBRT 10-year pelvic recurrence (PR) was more frequent in the VBT group (6.3% vs. 0.9%, p = 0.004) 10-years OS: 69.5% vs. 67.6%	HR for VR: 1.42 (95% CI 0.45 - 4.46) HR for PR: 6.65 (95% CI 1.50 - 29.48) HR for OS: 0.94 (95% CI 0.67 - 1.32)	VR p value: 0.55 PR p value: p = 0.004 OS p value: 0.72

PFS (progression free survival), OS overall survival), DFS (disease free survival), HR (hazard ratio), VR (vaginal recurrence), VBT (vaginal brachytherapy), EBRT (external beam radiotherapy)

There was a significant increase in progression-free survival (PFS), which was the primary endpoint (13.8 months for the placebo group versus a median time not achieved in the olaparib group). With a median follow-up of 41 months, the estimated rate of freedom from progression or from death at 3 years was 70% lower in the olaparib group (60% versus 27% in the placebo group, HR 0.30, 95%CI 0.23-0.41,  $p < 0.001$ ), confirmed by central investigator. There was also an expressive increase in the secondary endpoint that was second PFS, median time not reached in the olaparib group versus 41.9 months in the placebo arm (HR 0.50, 95%CI 0.35-0.72;  $p < 0.001$ ).

The most commonly adverse events are consistent with toxic effects reported for PARP inhibitors such as gastrointestinal disorders (nausea, vomiting, and diarrhea), fatigue, and anemia. Serious adverse events occurred in 21% of the patients in the olaparib group versus 12% in the placebo group, and 12% of the patients in the olaparib group discontinued the treatment due to toxicity.

Olaparib maintenance therapy demonstrated significant benefit in PFS in *BRCA* mutated patients with newly diagnosed advanced ovarian epithelial cancer.

#### **MITO16B-MaNGOOV2B-ENGOTOV17**

Bevacizumab in combination to first-line carboplatin and paclitaxel and as maintenance prolongs PFS in patients with stage IIIB-IV OC. It is also approved in bevacizumab-naive patients with platinum sensitive or resistant relapse. At ASCO 2018, it was presented a randomized, open label, phase III trial to test if the addition of bevacizumab to a platinum-based chemotherapy prolongs PFS for recurrent platinum sensitive ovarian cancer patients who have received bevacizumab in first line treatment<sup>(2)</sup>. They were randomized to 6 cycles of platinum-based doublets (carboplatin/paclitaxel, carboplatin/gemcitabine or carboplatin/pegylated liposomal doxorubicin) with or without bevacizumab administered concomitant with chemotherapy and as maintenance until disease progression. Four hundred and five patients were enrolled; 64% of patients had progressed  $\geq 12$  months after the last dose of platinum and 72% of patients after completion of first-line bevacizumab maintenance. Median PFS was 8.8 months and 11.8 months without and with bevacizumab, respectively (HR 0.51, 95%CI 0.41-0.64,  $p < 0.001$ ); median OS was 27.1 months and 26.7 months without and with bevacizumab, respectively (HR 1.00, 95%CI 0.73-1.39,  $p = 0.98$ ) (Table 1). Severe (grade 3 or 4) hypertension (27.5% versus 9.7%,  $p < 0.001$ ) and proteinuria (4% versus 0%,  $p = 0.007$ ) were more frequent in the bevacizumab arm. This trial shows that patients with platinum sensitive recurrent OC previously treated with bevacizumab in first line setting can be rechallenged with bevacizumab in combination with platinum-based doublets with no unexpected toxicity.

#### **AGO-OVAR 2.21/ENGOT-ov 18 trial**

Presented at ESMO 2018, this is the first prospective, randomized, phase III trial comparing two schemes containing bevacizumab in patients with platinum-sensitive recurrent ovarian cancer<sup>(3)</sup>. It is known that carboplatin/gemcitabine/bevacizumab significantly increases PFS over carboplatin/gemcitabine alone whilst carboplatin/pegylated liposomal doxorubicin has better toxicity profile compared to carboplatin/paclitaxel in patients with platinum-sensitive recurrent ovarian cancer. The aim of this trial was to evaluate whether carboplatin/pegylated liposomal doxorubicin is superior to carboplatin/gemcitabine when given in combination with bevacizumab. Primary endpoint was PFS and secondary endpoints were OS, biological progression-free survival by serum CA125, quality of life, safety and tolerability. Between 2013 and 2015, 682 patients were randomized to carboplatin/gemcitabine/bevacizumab ( $n = 337$ , standard arm, CGB) or carboplatin/pegylated liposomal doxorubicin/bevacizumab ( $n = 345$ , experimental arm, CDB). Prior bevacizumab was allowed. At data cut-off, 571 events occurred, CGB was associated with 359 (53.3%) serious adverse events versus 314 (46.7%) for CDB ( $p = 0.083$ ). Median PFS in the standard arm was 11.7 months (95% CI 11.1-12.8) versus 13.3 months (95%CI 11.7-14.3) in the experimental arm (HR 0.80; 95%CI 0.68-0.96,  $p = 0.0128$ ). In the stratum with previous anti-angiogenic treatment ( $n = 309$ ) median PFS was 10.1 months versus 11.3 months, respectively (HR 0.73; 95%CI 0.57-0.94,  $p = 0.0126$ ) (Table 1). CDB provided a significant PFS improvement compared to CGB in patients with platinum-sensitive recurrent ovarian cancer with fewer serious adverse events. Thus, this schema might be an important therapeutic option in this scenario. Future studies should compare other platinum doublets in combination with bevacizumab, including carboplatin and paclitaxel.

#### **GOG 213 - Secondary Cytoreductive Surgery**

Patients with limited platinum-sensitive recurrent ovarian cancer (PSOC) have secondary cytoreductive surgery (SCS) as an optional approach that should be considered. In 2017, the interim analysis of the DESKTOP III presented at the ASCO meeting supported this strategy<sup>(4)</sup>. However, this year during the ASCO meeting, the presentation of the second objective of the GOG213 gave a different perspective for the SCS<sup>(5)</sup>. This study was designed with two primary objectives: first to evaluate the addition of bevacizumab to the traditional carboplatin/paclitaxel in patients with PSOC (these results were published last year)<sup>(6)</sup> and second to determine if SCS followed by chemotherapy would improve OS of those patients. Exploratory objectives included access the effect of secondary surgery on platinum-free survival. To be included in the trial the patients must have had complete response to front-line therapy including: complete clinical, radiologic and CA125 responses; platinum-free interval  $\geq 6$  months; and clinically evident recurrence confirmed by biopsy and measurable.



From December 2007 until June 2017, 485 women were randomized to have SCS followed by platinum based chemotherapy (PBC) or PBC alone. The goal of the SCS was complete removal of all visible disease (R0) and 68% of the patients who underwent surgery achieved this goal. With a median follow-up of 34.6 months, there was no significant difference in OS between the two arms. The median OS was 53.6 months to the SCS group versus 65.7 months in the group treated exclusively with PBC (Table 1). Apparently, the addition of bevacizumab (84% of the patients) to the PBC has overcome the benefit of the SCS for those patients. The authors concluded that SCS with PBC was not associated with OS improvement when compared to chemotherapy alone.

### Endometrial carcinoma: efficacy based in subgroups of the PORTEC 2 trial

Relatively few clinically important therapeutic advances have occurred in the treatment of endometrial cancer. PORTEC 2 is one of the most important trial on this subject and has been updated with 10-year follow-up. This was a randomized clinical trial in high-intermediate risk (HIR) endometrial cancer (>60 years with either a grade 3 or > 50% myometrium invasion) comparing external beam radiotherapy (EBRT) with vaginal brachytherapy (VB). They evaluated long-term outcomes combined with pathology review and molecular analysis. Four hundred forty seven women with HIR endometrial cancer were randomized between 2000-2006 to VB or EBRT. Exclusion criteria were serous or clear cell carcinoma; staging lymphadenectomy; >8 weeks interval between surgery and radiotherapy; history of previous malignance; previous pelvic radiotherapy, hormonal and chemotherapy; Crohn's disease or ulcerative colitis. Primary endpoint was vaginal recurrence (VR). With a median follow up of 116 months, 10 year VR was 3.4% versus 2.4% for VB vs. EBRT ( $p=0.55$ ); 10 year pelvic recurrence (PR) was more frequent in VB group (6.3 versus 0.9%  $p=0.004$ ), mostly combined with distant metastasis (DM). Ten-year isolated PR was 2.5 versus 0.5% ( $p=0.1$ ) and DM 10.4 versus 8.9% ( $p=0.45$ ). OS for VB versus EBRT was 69.5 versus 67.6% ( $p=0.72$ ) (Table 1). L1CAM or p53 mutant expression and substantial lymph-vascular space invasion were risk factors for PR and DM, favoring EBRT in these cases. Ten-year long-term of PORTEC 2 confirm VB as standard adjuvant treatment for HIR endometrial cancer. Patients with either lymph-vascular invasion, L1CAM or p53 expression should be further evaluated in a prospective clinical trial before being used as standard for choosing between adjuvant EBRT or VB.

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