GYNECOLOGIC CANCER GROUP
SINGAPORE

Gynecologic Cancer Group Singapore (GCGS) Guidelines for the Treatment of Early and Advanced Epithelial Ovarian Cancer

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Abstract

Introduction: The Gynecologic Cancer Group Singapore (GCGS) aimed to develop a set of clinical practice guidelines for the management of early and advanced epithelial ovarian cancer.

Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting.

Results: Five international guidelines were evaluated, namely the US National Comprehensive Cancer Network (Version 1.2020), the European Society of Medical Oncology (2013 as well as the updated ESMO–ESGO consensus conference recommendations 2019), the Scottish Intercollegiate Guidelines Network (2018), Clinical Guidelines Network Cancer Council Australia 2014 and Singapore Cancer Network (SCAN) clinical practice guidelines 2015. Recommendations on the role of systemic therapy with intravenous chemotherapy, intraperitoneal chemotherapy, anti-angiogenic agents, poly (ADP-ribose) polymerase (PARP) inhibitors, neoadjuvant chemotherapy as well as the role of genetic testing in patients with epithelial ovarian cancer were developed.

Conclusion: These guidelines which are contextualised to the Singapore practice setting form the GCGS treatment guidelines of epithelial ovarian cancer 2020.

Key words: Clinical practice guidelines, Chemotherapy, Anti-angiogenics, PARP inhibitors

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Introduction

Epithelial ovary cancer (EOC) is often diagnosed in advanced stages and is the fifth most common cancer and the seventh most common cause of cancer mortality amongst females in Singapore. A total of 1874 new cases of ovarian cancer were diagnosed between 2013 and 2017. The incidence of ovarian cancer has been rising from 6.0 per 100,000 (1968 to 1972) to 13.1 per 100,000 (2013 to 2017). [1] Treatment of advanced EOC frequently involves a combined approach with cytoreductive surgery and chemotherapy as the mainstays of primary therapy. Cytoreductive surgery aims to remove all macroscopic disease as resection has consistently been shown by retrospective studies to be associated with improved progression-free survival (PFS) and overall survival (OS). [2,3]. For the last 15 years, the gold standard of care has been to administer platinum-taxane chemotherapy intravenously every 3 weeks after debulking surgery. However, the optimal method of administering platinum-taxane chemotherapy remains to be determined. In recent years, more data has emerged helping to guide variables such as the scheduling (dose-dense vs 3-weekly), route of drug administration (intraperitoneal (IP) vs intravenous (IV)) and the timing of chemotherapy (neoadjuvant vs frontline) have challenged the conventional platinum-taxane regimen. The use of targeted therapy as well as maintenance strategies with use of bevacizumab and PARP inhibitors have gained traction in recent years.

The GCGS Guidelines for the treatment of early and advanced EOC

The GCGS Guidelines are clinical practice guidelines for the treatment of newly diagnosed early and advanced EOC. It includes guidelines for the treatment of early and advanced epithelial ovarian cancer but excludes carcinosarcoma and non-epithelial cancer of the ovary. The first edition of these guidelines is intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of early and advanced EOC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with ovarian cancer.

Guideline Recommendations/Development

The Gynecological Cancers Group Singapore (GCGS) guidelines workgroup comprises a panel of 13 medical oncologists and gynaecology oncology surgeons from Singapore with special interests in the management of gynaecological cancers. Membership of the workgroup was by invitation. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Singapore Cancer Research Institute. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the

workgroup members. In view of the prevailing COVID-19 pandemic, the group met once virtually via videoconferencing, and completed guideline development through email communication.

The ADAPTE framework [4] was used as a pragmatic structure and guidance for calibration of international high-quality guidelines to the Singapore context. The framework involves three phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and recognising possible dissent amongst workgroup members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalization phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation.

These guidelines set out to answer the following questions pertaining to management of women with advanced EOC:

1: What is the optimal adjuvant chemotherapy regimen for advanced EOC following primary cytoreductive surgery?

2: What is the role of neoadjuvant chemotherapy in advanced EOC?

3. What is the role of IP chemotherapy in women with optimally debulked advanced EOC?

4: What is the role of HIPEC in optimally debulked EOC?

5: What is the role of front-line Bevacizumab in advanced EOC?

6: What is the role of PARP inhibitor therapy in advanced EOC ?

7: Should secondary debulking surgery be offered to patients with recurrent ovarian cancer?

8: Genetic testing in ovarian cancer - Who should be referred for genetic testing?

Five international guidelines were selected for review

(Supplementary Table 1):

- “NCCN Guidelines for Ovarian Cancer Version 1.2020” by the National Cancer Comprehensive Network (NCCN, USA) [5]
- “Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO), 2013 [6] as well as ESMO–ESGO consensus conference recommendations, 2019 [7]
- “SIGN 135. Management of Epithelial Ovarian Cancer. A National Clinical Guideline” by the Scottish Intercollegiate Guidelines Network (SIGN, UK), 2018 [8]
- “Clinical Guidelines Network Cancer Council Australia 2014” [9]

- Singapore Cancer Network (SCAN) clinical practice guidelines for front-line systemic therapy of advanced epithelial ovarian cancer 2015 [10]

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of advanced EOC, it will be reviewed earlier.

Advanced EOC:

Qn1: What is the optimal adjuvant chemotherapy regimen for advanced EOC following primary cytoreductive surgery?

There is unanimous agreement amongst the working group members that platinum-taxane remains the standard of care for front-line chemotherapy. The workgroup voted 10 to 1 in favour of the adoption of the SIGN guidelines for front-line IV chemotherapy following cytoreductive surgery due to its comprehensive nature. Members were initially divided over the adoption of NCCN or SIGN guidelines especially in patients with poor ECOG status given the results of the EWOC study where carboplatin single agent was reported to be less active with significant worse survival outcome in vulnerable elderly pts compared to 3-weekly and weekly carboplatin regimens. (DOI: 10.1200/JCO.2019.37.15_suppl.5508

Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 5508-5508. Published online May 26, 2019.) Several members felt SIGN guidelines had a better explanation/rationale over NCCN and majority consensus was to endorse SIGN guidelines which also recommend:

• Discussion of dose-dense chemotherapy as a treatment option with patients

• Pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin in cases of taxane-intolerance

• Against the addition of a third cytotoxic agent to platinum-taxane

• Single-agent carboplatin in patients who are unable to tolerate combination chemotherapy

The workgroup acknowledges that there is no local data regarding front-line IV chemotherapy for advanced EOC. Multiple Phase III trials (ICON8, GOG262 and MITO7) after JGOG 3062 failed to demonstrate superiority of dose-dense Paclitaxel-Carboplatin chemotherapy. [11-14] Hence, the workgroup endorsed the SIGN guidelines which recommend dose-dense chemotherapy as a treatment option to be discussed with patients, where increased toxicities and increased hospital visits need to be factored.

The workgroup also endorsed the NCCN guidelines' recommendation of pegylated liposomal doxorubicin-carboplatin as a regimen that may be useful in select patients at high risk for neurotoxicity or those who would like to avoid alopecia. This is based on the Phase III MITO-2 trial which randomized 820 patients with Stage III or IV ovarian cancer to either Paclitaxel-carboplatin or pegylated liposomal doxorubicin-carboplatin and found no significant difference in median overall survival (53.2 and 61.6 months, respectively, HR 0.89; 95% CI, 0.72 – 1.12, P=.32) [15]. More haematologic adverse events but less neurotoxicity and alopecia were observed in the pegylated liposomal doxorubicin-carboplatin group.

Qn2: What is the role of neoadjuvant chemotherapy in advanced EOC?

The workgroup voted 10 to 1 to continue endorsing the NCCN guidelines which recommend a multidisciplinary approach to patient selection and accommodates for treating oncologist to judge most suitable neoadjuvant chemotherapy regimen.

There remain two seminal Phase III trials on neoadjuvant chemotherapy in advanced EOC. The EORTC 55971 randomised 718 women with stage III or IV ovarian cancer to neoadjuvant chemotherapy followed by interval debulking surgery or primary debulking surgery. There were no significant differences between the study groups with regards to OS (HR = 0.98; 95% CI, 0.82 to 1.18) or PFS (HR = 1.01; 95% CI, 0.86 to 1.17). [16] In the EORTC 55971 study, there was increased debulking rate and reduced surgical complications in the neoadjuvant chemotherapy group. In the CHORUS study, a phase III randomised trial to investigate the timing of initial surgery in ovarian cancer,43 patients with clinical stage III or IV ovarian cancer were randomised to primary surgery followed by 6 cycles of platinum-based chemotherapy or 3 cycles of neoadjuvant chemotherapy followed by surgery before another 3 cycles of platinum-based chemotherapy. [17] CHORUS was designed to demonstrate non-inferiority of neoadjuvant chemotherapy based on a 3-year survival of 50% with primary debulking surgery. A total of 550 women were randomised. Median tumour size was 8 cm, 25% FIGO IV and 19% World Health Organization (WHO) performance status 2. At a median follow-up of 3 years, the OS is superior for the neoadjuvant chemotherapy group (24.5 months vs 22.8 months; HR = 0.87; 80% CI, 0.76 to 0.98).

No cost-effectiveness analysis was done.

With regard to the EORTC 55971 trial, we are mindful of the fact that the accrued patients have very extensive and bulky disease as 73% had tumours of >5 cm and 47% had tumours of >10 cm at randomisation. Similarly, the median size of tumour in the CHORUS trial was 8 cm. Hence, the results of the trials on the role of neoadjuvant chemotherapy cannot be extrapolated to patients with less bulky disease. Furthermore, in a posthoc analysis in the EORTC trial, amongst patients with metastatic disease <5 cm in diameter at randomisation, the OS was slightly longer in the primary surgery group than in the neoadjuvant chemotherapy group (HR = 0.64; 95% CI, 0.45 to 0.93).

Later phase III trials (JCOG 0602 and SCORPION) have also failed to demonstrate non-inferiority and superiority of the neoadjuvant approach, respectively. [18,19] Hence, rather than recommending neoadjuvant chemotherapy as an alternative for ovarian cancer patients with any stage or disease bulk, it is preferable to reserve neoadjuvant chemotherapy for selected patients with bulky stage III or IV disease, at the same time taking into account the resectability, age, stage, histology and performance status.

Although the pooled analysis of EORTC 55971 and CHORUS trials suggested that stage IV disease with bulky tumors had longer survival with neoadjuvant therapy, more data will be necessary prior to recommending neoadjuvant chemotherapy in patients with potentially resectable ovarian cancer, and upfront debulking surgery remains the treatment of choice. [20] We await results of the ongoing TRUST study to further shed light on this. [21]

Qn3. What is the role of IP chemotherapy in women with optimally debulked advanced EOC?

Majority of the workgroup recommends IP chemotherapy in the context of clinical trial. Three members argued in favor of the use of NCCN guidelines which provides the option that selected patients with low volume residual disease may be considered for IP chemo. Patient selection is of utmost importance as patients being considered for IP chemotherapy need to be fit, with good performance status and renal function.

GOG-172 previously demonstrated a benefit in PFS and OS for IP chemo. [22] Additionally a meta-analysis of five clinical trials confirmed a benefit for intraperitoneal chemotherapy in OS. This led to a National Cancer Institute alert in 1996 recommending that intraperitoneal therapy should be considered in patients with small volume (<1 cm) or no residual disease after surgery. [23] However, this treatment has not been adopted as a standard of care in most institutions and countries due to its greater toxicity and difficulty in delivering all the planned treatment.

The workgroup agreed that IP treatment has not been adopted as standard of care in view of its greater toxicity and difficulty delivering all the planned treatment. IP chemo is more complex to administer and also that there is a lack of experience and familiarity with the procedure locally. Lack of current standard intravenous chemotherapy (Paclitaxel/Carboplatin three-weekly or dose-dense Paclitaxel/Carboplatin) in the standard arms of the IP trials has made the interpretation of the results difficult. In GOG 252, duration of PFS was not significantly increased with either IP regimen (compared with the IV carboplatin reference arm) when combined with bevacizumab and was better tolerated than IP cisplatin. [24]

We await further trial data from the iPOCC study looking at the role of IP chemotherapy as compared to dose dense chemotherapy in the Asian setting. [25]

Qn4: What is the role of HIPEC in optimally debulked Epithelial Ovarian Cancer?

The OVHIPEC-1 trial investigated the role of HIPEC in upfront unresectable stage IIIC EOC. [26]. This trial showed an improvement in the primary PFS endpoint (mean PFS 10.7 months vs. 14.2 months, p= 0.003) and secondary endpoint of mean OS (33.0 months vs 45.7 months, p = 0.02) for HIPEC compared to the no-HIPEC group, respectively. Multiple criticisms of this study including

- Inadequate power of the study (sample size was adjusted due to slow accrual,
- small sample size of patients recruited over 9 years over several participating sites
- timing of randomisation (initially randomization prior to first cycle chemo then subsequently amended to include both prior to chemotherapy or prior to interval debulking surgery),
- the selection of sites and quality assurance of the surgeons at each site,
- need to pre-plan considering longer OT time,
- longer hospitalisation,
- increase number of patients in the HIPEC arm requiring a stoma,
- inadequate reporting of adverse events.

In contrast, another randomized controlled trial by Lim et al did not show a survival benefit with HIPEC compared to surgery alone. [27]

Most of the workgroup (9 members) were in agreement with current ESMO recommendations that HIPEC in the upfront setting should not be considered as standard therapy and be limited to well-designed prospective trials. HIPEC can be discussed on individual basis in selected groups (given limitations of the OVHIPEC-1 trial). Two members felt the option of HIPEC in this setting can be left open to discussion with the patient as per the NCCN guidelines which indicate that HIPEC can be considered for all patients with stage III disease for which NACT and IDS is performed, without any further requirements for selection of patients.

Qn 5: What is the role of front-line Bevacizumab in Advanced Epithelial Ovarian Cancer?

The workgroup has voted (11 out of 11 members) in favour of the European Society of Medical Oncology guidelines but recommends the careful selection of patients when considering the use of upfront bevacizumab. Patients with poor prognostic features such as stage IV or suboptimal debulking as defined in the ICON-7 trial should be considered for upfront bevacizumab. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of one year. The dose of bevacizumab is 7.5 mg/kg as used in the ICON7 regimen [28] or 15mg/kg as used in GOG218 although the majority preferred to use the lower dose given the lack of any data suggesting inferiority of the 7.5mg/kg dose vs 15mg/kg and the significant difference in economic impact on patients when the drug is not fully reimbursed.

Qn 6: What is the role of PARP inhibitor therapy in advanced EOC?

Ovarian cancer is the leading cause of death from gynecologic tumors in the Western world. [29] Approximately 80% of patients with newly diagnosed ovarian cancer have a response to platinum-based chemotherapy. Unfortunately, most patients have relapses, and responses to subsequent therapies are generally short-lived [30-33]. Maintenance therapy has been shown to prolong control of ovarian cancer, [34] and disease control has also been prolonged with the combination of bevacizumab and chemotherapy in patients receiving first-line treatment and in those with platinum-sensitive relapsed ovarian cancer. [35,36]

Members of the poly (adenosine diphosphate–ribose) polymerase (PARP) family of enzymes are central to the repair of DNA single-strand breaks. [37] Thus, PARP inhibition leads to the formation of double-stranded DNA breaks that cannot be accurately repaired in tumors with homologous recombination deficiency, [38,39] owing to multiple mechanisms, including the synthetic lethality that results from unresolved DNA damage and the replication arrest that results from physical obstruction of replication forks by PARP trapping. [38,40]

The incorporation of PARP inhibitors in the treatment paradigm of ovarian cancer was evaluated in upfront maintenance setting in the PRIMA/ENGOT-OV26/GOG-3012 study, PAOLA and SOLO1 study [41-

43], in the recurrent platinum sensitive setting in Study19, ENGOT-OV16/NOVA, SOLO2, Ariel3. [44-48] While in the treatment setting, monotherapy PARP inhibitors were explored specifically in the subset of patients harbouring a *BRCA1/2* mutation in both SOLO3 21 and ARIEL2 study [49].

Recommendations for PARP inhibitors in the maintenance setting following upfront chemotherapy

Seven members in the workgroup voted in favor to adopt the NCCN guidelines while 3 members voted to adopt the ESMO guidelines. The NCCN guidelines was preferred by the majority of the panel as it was updated to include the latest PARP inhibitor evidence in the upfront maintenance setting. In the homologous recombination (HR) proficient women, the workgroup recommended niraparib can be considered for women who had a response to frontline platinum-based chemotherapy (including women with unknown HRD status). [41] However, it was emphasized that the risks and benefits of PARP inhibitor therapy should be discussed with patients given the significant costs with long term maintenance use of these agents.

For women with HR deficient EOC, the workgroup recommended to consider PARP inhibitor niraparib following response to frontline platinum-based chemotherapy. [41] The combination of Olarapib and bevacizumab can be considered after response is observed from the use of bevazicumab in combination with frontline platinum-based chemotherapy [42]. While the PARP inhibitor Olaparib was recommended for use in the maintenance setting for patients harbouring *BRCA1/2* mutation [43].

Recommendations for PARP inhibitors in the maintenance setting in advanced platinum sensitive recurrent ovarian cancer

The workgroup recommends consideration of monotherapy maintenance PARP inhibitor therapy with Olaparib, Niraparib or Rucaparib after response to platinum chemotherapy for all patients with relapsed platinum sensitive EOC. [44,45,46, 47]

Recommendations for PARP inhibitors in the treatment setting as monotherapy

The workgroup endorses the ESMO–ESGO guidelines to consider PARP inhibitors Olaparib 21 and Rucaparib 22 as monotherapy in women with EOC that harbors *BRCA1/2* mutation who have been treated with ≥ 2 lines of chemotherapy. [48,49] The workgroup also agrees with ESMO–ESGO guidelines that the benefit of continuing PARP inhibitor therapy beyond progression has not been demonstrated conclusively and more studies are needed in this area.

Qn7: Should secondary debulking surgery be offered to patients with recurrent ovarian cancer?

The workgroup agreed that complete cytoreductive surgery followed by systemic treatment improves PFS and OS and extends benefit to the next line of treatment in selected patients with first recurrence of ovarian cancer (based on AGO DESKTOP III) with median OS from 46 to 53.7 months (HR 0.75, 95% CI 0.58-0.96, P=0.02), though the benefit was restricted for the group that achieved a complete resection. [50] The lack of PFS and OS benefit reported by Coleman et al [51] contrasts with results of AGO-DESKTOP III but notably patient selection in GOG 213 was not as stringent as in AGO – GOG213 used “investigator determined resectability” vs AGO score in DESKTOP III. The complete resection rate was 67% in GOG213

versus 74% in DESKTOP III. Bevacizumab used in 84% of patients and could have impacted on post-operative outcomes.

Patients should have a high probability of a complete resection and the following predictors for resection should be considered:

- platinum treatment-free interval (TFI) of >6 months,
- positive AGO score [good PS, complete resection at primary surgery and the absence of large volume (>500 mL) ascites],
- absence of probably unresectable lesions on imaging
- absence of contraindications to surgery (e.g. comorbidities, prior severe complications of surgery)

The role of complete cytoreductive surgery in second or later recurrence may provide benefit in selected patients and specialised centres. (based on ESMO Recommendations 17.2)

There was discussion among the group over the recommendations of use of HIPEC in recurrent ovarian cancer. Majority felt that HIPEC added to cytoreductive surgery in recurrent ovarian cancer has not been proven to be beneficial in appropriately designed prospective studies and were in favor of the ESMO recommendations that HIPEC in the recurrent setting be considered in clinical trial settings. Two workgroup members opined that the role of HIPEC in recurrent setting could be discussed with selected patients.

Qn 8: Genetic testing in ovarian cancer - Who should be referred for genetic testing?

The strongest risk factor for ovarian cancer is a family history of breast or ovarian cancer, and approximately 25% of all ovarian cancers are caused by a heritable genetic condition.[52] Of these, mutations in *BRCA1* and *BRCA2* account for almost 40% of ovarian cancers in women with a family history of the disease,[53] and approximately one quarter (6% of all ovarian/fallopian tube/peritoneal cancers) are caused by genes other than *BRCA1* and *BRCA2*, including many genes associated with the Fanconi anemia pathway or otherwise involved with homologous recombination. Knowledge about underlying molecular alterations in ovarian cancer could allow for more personalized diagnostic, predictive, prognostic, and therapeutic strategies for the patient but also have clinical implications for her family members.[54,55] Many medical societies recommend genetic testing for all women diagnosed with ovarian cancer, yet only approximately 30% of women undergo any genetic testing.[55]Moreover, oncology providers often still have an insufficient understanding and/or a lack of resources and strategies for how to best incorporate genomic testing into their practice.

The workgroup recommends that all women diagnosed with non-mucinous epithelial ovarian, primary peritoneal and fallopian tube cancer should receive genetic counseling and be referred for germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes even in the absence of a family history. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1/2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the

recurrent setting. Validated somatic molecular testing (where available) should be considered where available and should include microsatellite instability or somatic tumor testing for mismatch repair deficiency (dMMR) and homologous recombination deficiency (HRD). Women with identified dMMR should be offered FDA-approved treatment based on these results. In the absence of *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy.

Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer. First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing [57]. Clinical decision making should not be made based on a variant of uncertain significance. Women with epithelial ovarian cancer should have testing at the time of diagnosis [57].

Conflicts of Interest

None

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