Epithelial Ovarian Cancer

Epithelial Ovarian Cancer Seminar: Overview on Current Management and Future Directions

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Summary

Epithelial ovarian cancer (EOC) generally presents at an advanced stage and is the most common cause of gynecologic cancer death. Treatment requires expert multidisciplinary care. Population based screening has been ineffective to date but new approaches for early diagnosis and prevention that leverage molecular genomics are in development. Initial therapy includes surgery and adjuvant therapy. EOC is composed of distinct histologic subtypes with unique genomic characteristics, which are improving the precision and effectiveness of therapy, allowing discovery of predictors of response such as *BRCA1/2* mutations, homologous recombination (HR) deficiency for DNA damage response pathway inhibitors, or resistance (CCNE1). Rapidly evolving techniques to measure genomic changes in tumour and blood allow assessment of sensitivity and emergence of resistance to therapy, and may be accurate indicators of residual disease. Recurrence unfortunately remains usually incurable, and patient symptom control and quality of life are key considerations at that time. Treatments for recurrence have to be designed from a patient's perspective, and incorporate meaningful measures of benefit. Urgent progress is needed to develop evidence and consensus-based treatment guidelines for each subgroup, and requires close international cooperation in conducting clinical trials through academic research groups such as the Gynecologic Cancer Intergroup.

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Since the last seminar publication 4 years ago[1], there have been major improvements in understanding invasive epithelial ovarian cancer (EOC) biology (**Figure 1**), and this has led to changes in clinical practice. This manuscript will summarize current optimal evidence-based approach to management of EOC.

Epidemiology and Risk Factors

EOC is the most lethal gynecologic cancer. Annually worldwide, 230,000 women will be diagnosed and 150,000 will die[2]. It represents the seventh most commonly diagnosed cancer among women in the world with 46% survival 5 years after diagnosis[3]. One of the main factors contributing to the high death-to-incidence rate is the advanced stage at the time of diagnosis. Late stage presentation has 5-year relative survival rate of 29%, in contrast to 92% for early stage disease[4]. Unfortunately, due to its asymptomatic nature, ~75% of patients are diagnosed at an advanced stage. Genomic predisposition to EOC is now well recognized in up to 15% of affected women. Breast cancer susceptibility genes (*BRCA*) 1 and *BRCA2* have been identified as causative genes involved in 65–75% of hereditary EOC. Deleterious mutations in *BRCA1/2* and other double-strand DNA break repair genes are largely associated with the high grade serous EOC subtype susceptibility. Lynch syndrome, an autosomal dominant hereditary cancer family syndrome accounts for 10–15% of hereditary EOC[5,6] and is typically associated with endometrioid or clear cell tumours[4]. Additional genetic syndromes include Peutz-Jegher and rare disorders[7]. Risk factors for EOC include the number of lifetime ovulations (absence of pregnancy, early age of menarche and late age at menopause), family history of EOC, smoking, benign gynecologic conditions including endometriosis, polycystic ovary syndrome and pelvic inflammatory disease[4], and potentially talc[8].

Screening

Considerable efforts have been made to implement screening of the general population to diagnose EOC early, but currently there is no approved strategy[9]. UKCTOCS, a randomised controlled trial of over 200,000 women assessing annual multimodal screening with serum cancer antigen (CA125), did not identify significant mortality reduction when the risk-for-ovarian-cancer algorithm was used, versus annual transvaginal ultrasound screening, versus no screening. Further follow-up is underway to assess late benefit due to a significant stage shift in women diagnosed with invasive ovarian/tubal/peritoneal cancer with multimodal screening compared to no screening[10]. Additional biomarker combinations such as Human epididymis protein 4 (HE4), a glycoprotein secreted by Mullerian epithelia of the female reproductive tract, have been tested with CA125[11] but further studies are required. A study screened 4348 women with ≥10% lifetime risk of ovarian or fallopian tube cancer using the risk of ovarian cancer algorithm (ROCA) and transvaginal sonography demonstrating evidence for stage shift with 53% of cancers detected during the trial being early stage compared to only 6% of cancers detected >1 year after the trial screening finished[12]. Longer follow-up will determine impact of this strategy on survival. The current recommendation for unaffected individuals with a high familial risk of ovarian cancer remains risk-reducing salpingo-oophorectomy by an age that depends upon their individual genetic predisposition. Efforts are also underway to improve genomic screening strategy[13].

Diagnosis

EOC symptoms are not specific and include abdominal bloating, early satiety, nausea, abdominal distension, change in bowel function, urinary symptoms, back pain, fatigue and loss of weight, which typically present months prior to diagnosis[14]. Initial investigations include the measurement of CA125 concentrations and pelvic ultrasound. To accurately define EOC extension, further imaging should include chest and abdomen/pelvis CTs for staging, and potentially a pelvic MRI. Optimal staging is surgical and includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, inspection of peritoneal surfaces with biopsy or removal of any suspicious areas, and para-aortic and pelvic lymph node dissection. Surgery should be performed by a trained gynaecological oncology surgeon with the goal of no residual disease. The staging procedure will establish the surgical stage, conventionally using International Federation of Gynecology and Obstetrics staging of ovarian cancer (FIGO stage) or AJCC-TNM classifications[15,16].

Pathologic diagnosis on tumor tissue is essential as ovarian cancer has different histology subtypes with different treatment approaches. Over the last decade it has become clear that EOC consists of a number of diseases (**Figure 2**) with distinct precursor lesions, tissues of origin, molecular biology, clinical presentation, chemosensitivity and patient outcome.

First Line Treatment Approach

Surgery

Primary debulking surgery (PDS) followed by chemotherapy has become the standard of care in advanced EOC since the eighties, despite the lack of upfront randomized trials defining its actual benefit[17]. No residual tumour (R0) after PDS is the most important prognostic factor for survival[18]. Two randomized clinical trials comparing PDS and chemotherapy with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS), showed similar survival with a low operative morbidity when the latter strategy was used[19,20]. Both trials have been criticised for their low R0 rates and low survival rates. However, it should be noted that the majority of the patients had extensive stage IIIC or IV disease. To help the debate, the TRUST trial randomising NACT versus PDS in advanced EOC is on-going in selected centres with 50% or more R0 rates (NCT02828618). At present the choice between PDS and chemotherapy or NACT and IDS remains controversial[21]. Further research is needed on how to select patients for PDS or NACT, including better and validated imaging or laparoscopic scoring systems and algorithms to predict operative morbidity.

A guideline for selecting patients with FIGO stage IIIC/IV for PDS or NACT followed by IDS is presented in Table 1[22]. The algorithm and guideline are based on the EORTC 55971 randomized trial [20] showing that patients with stage IIIC disease and small metastases (<5 cm) had better overall survival (OS) with PDS whereas patients with stage IV disease had better survival with NACT. At the time of surgery, it is of outmost importance to remove all visible or palpable tumour at PDS and IDS[18,20]. For decades the role of a full pelvic and para-aortic lymphadenectomy in advanced EOC has been advocated[23]. However, a recent randomized study from AGO-OVAR has shown that systematic pelvic and para-aortic lymphadenectomy in patients with advanced EOC with both intra-abdominal complete resection and clinically negative lymph nodes does not improve overall or progression-free survival (PFS)[24].

In patients with stage 1A low grade disease opting for fertility conservation surgery, the uterus and contralateral ovary can be left in place pending pathology review of the removed tissues and further discussion with the patient. The selection of patients for fertility preservation requires very careful consideration of the risks and benefits between the surgical oncologist and patient. The likelihood of cure is high for women with stage 1A disease, but residual disease and subsequent recurrence are associated with low likelihood of salvage. Pathologic differences greatly influence the potential for conservative surgery and this option is best reserved for women with well-differentiated or low grade, Stage IA disease[25].

Systemic Therapy

The treatment guidelines for EOC have largely been driven by HGSOC and first line therapy has largely been established based on this subgroup.

- *Early Stage*

Randomized clinical trials in early stage disease have been challenging to conduct as a minority of patients present early. ICON and ACTION randomized trials support the use of adjuvant chemotherapy in early stage disease, with carboplatin/cisplatin and paclitaxel, with level IA evidence[26-31]. Subset analyses raised the question of a potential to avoid chemotherapy in well-staged early stage patients, but this finding should be considered as exploratory[32]. The question of adjuvant therapy for early stage can be discussed based on histology subtype and grade[33]. The GOG157 trial compared 3 versus 6 cycles of adjuvant paclitaxel and carboplatin but was powered to detect a 50% decrease in the recurrence rate at 5 years[34]; there was no difference in the arms, perhaps supporting reduction in the number of cycles, with reduced toxicity in well-staged patients. However, the standard recommendation in practice remains 6 cycles of platinum adjuvant therapy.

- *Advanced Stage*

Intravenous (IV) 3-weekly carboplatin (Area under the curve (AUC) 5-6) and paclitaxel (175 mg/m² over 3 hours) remain the standard chemotherapy drugs for first-line therapy in advanced stage EOC[35]. Weekly IV paclitaxel has recently been investigated and might be an alternative to 3-weekly paclitaxel in combination with 3-weekly IV carboplatin. In the JGOG 3016 study, 631 women with stage II-IV EOC were randomized between carboplatin AUC 6 with paclitaxel 180 mg/m^2 every 3 weeks and carboplatin AUC 6 every 3 weeks with weekly paclitaxel 80 mg/m^2. A sustained significant improvement in PFS and OS for patients receiving dose-dense therapy compared with conventional treatment was reported[36]. However, a benefit in PFS was not seen in three other trials with weekly paclitaxel[37-39], possibly due to pharmaco-genomic influences since the initial JGOG 3016 trial was in a Japanese population whereas the subsequent trials were predominantly in Caucasian populations.

Two randomized trials, GOG218 and ICON7 showed a significantly increased PFS, but not OS with the addition of the anti-angiogenesis inhibitor bevacizumab (directed against vascular endothelial growth factor, VEGF), to 3 weekly paclitaxel and carboplatin followed by maintenance bevacizumab[40,41]. In a pre-planned analysis of the ICON7 study[41], the addition of bevacizumab in women at high risk of progression (stage III disease with >1 cm residual disease following PDS, inoperable patients with stage III, and stage IV disease), significantly improved estimated median PFS (10.5 months with standard

therapy versus 15.9 months with bevacizumab (HR 0.68; 95% CI, 0.55-0.85; p<0.001) and median OS (28.8 versus 36.6 months (HR 0.64; 95% CI, 0.48-0.85; p=0.002)). These findings led to the addition of bevacizumab to 3-weekly paclitaxel and carboplatin as standard of care in this high-risk population in many countries. AGO trials group exploring 15 versus 30 cycles[42-44] will confirm or refute the hypothesis from ICON7 and ROSIA trials that benefit of bevacizumab is related to the maintenance duration.

The use of intraperitoneal (IP) cisplatin and paclitaxel has resulted in a survival advantage in several trials in patients with <1 cm residual tumour after PDS[45-47]. These trials have been criticized because they were hampered by outdated control arms, experimental IP chemotherapy arms, various changes (e.g. different dose, dose dense regimens) and higher toxicity[48]. The role of IP therapy has recently come into question with GOG252 study, assessing IV dose dense versus IP therapy with the addition of bevacizumab which did not show any benefit in PFS for patients with FIGO stage III disease and <1 cm residual tumour following PDS[49]. Overall, the picture seems to demonstrate that dose for dose, there is no advantage of IP chemotherapy over IV. Studies which were associated with benefit of IP chemotherapy used IP cisplatin at 100mg/m^2 and were associated with a higher incidence of toxicity.

Hyperthermic IP chemotherapy (HIPEC) until recently had no proven benefit in EOC[50]. However, in 2017, two randomized studies from Dutch and Korean groups used HIPEC at the time of IDS after NACT[50-52]. The Dutch trial reported significant advantage for the HIPEC group, which was not observed in the Korean trial. In the Dutch trial, the median recurrence-free survival and median OS were 10.7 and 33.9 months in the surgery group versus 14.2 and 45.7 months in the surgery-plus-HIPEC group, respectively. In women who received NACT in the Korean trial, the median PFS for HIPEC and control group were 20 and 19 months, respectively (log-rank test, p = 0.137) and the median OS for HIPEC and control group were 54 and 51 months, respectively (log-rank test, p = 0.407). These trials were small and resulted in higher toxicity when HIPEC was used and should be confirmed before HIPEC can be used as standard of care[53]. The key question of whether benefit is related to an additional IP cycle of therapy or the potential association with hyperthermia is going to be evaluated in a prospective trial (personal communication with Dr. Gupta, Tata Memorial Institute).

Follow-up

Follow-up may identify disease recurrence earlier, but there are no clear guidelines on the type and frequency; regular physical examination is generally recommended. The earliest indication of recurrent disease might be CA125 in patients where this has been a marker of disease. With neither radiological nor clinical evidence of disease, recurrence can be defined by the rise >2× the upper limit of normal (ULN is 35 U/mL) for patients with normal baseline CA125 levels or for those whose CA125 levels have normalized during treatment, or CA125 level >2× nadir value (on 2 successive occasions) for patients whose CA125 levels have not normalized. The question of value from close monitoring to detect recurrence early remains, as no survival benefit was observed with early treatment of relapse based on increased CA125 alone[54]. This might have been due to the lack of effective therapeutic options at recurrence, or a limitation of the study, which was underpowered to detect a potential survival benefit in patients eligible for secondary cytoreduction. Although early detection may not have survival advantage, it does allow for exploration of treatment options, including surgery or experimental therapies, which have led to regular follow-up after completion of primary therapy.

CT scans can detect an asymptomatic recurrence and should be systematically performed to establish a baseline before starting new lines of therapy. Several studies have demonstrated the utility of FDG-PET/CT for early detection of recurrent EOC and MRI in the evaluation of patients with recurrent EOC and its potential role of prediction of optimal secondary debulking surgery (SDS)[55].

Recurrence

Unfortunately, recurrence is incurable in ~75% of women who present with advanced disease. A functional algorithm utilizing the platinum-free interval (PFI) to select subsequent therapy has been a simple and remarkably effective way of choosing therapy and inferring prognosis for last 30 years. Recently, the Gynecologic Cancer Inter Group (GCIG) redefined the conventional practice of using PFI to categorize patients as platinum-sensitive or resistant, and replaced this by a therapy-free interval (TFI), with the remaining cut-off at 6 months[56].

At the time of relapse, SDS should be considered for appropriate patients[57]. AGO-OVAR developed DESKTOP score as a predictive algorithm of effective SDS[58]. Patients with the first recurrence and a PFI of >6 months (platinum sensitive) EOC have a positive DESKTOP score when accompanied by good performance status (ECOG 0), complete resection during first line therapy and ascites of less than 500mL; these patients have a significantly better PFS when undergoing SDS followed by chemotherapy, versus chemotherapy alone[59]. A positive DESKTOP score predicted the probability of complete resection in more than 2 out of 3 patients with 95% accuracy[58]. The Tian Risk model, which is also based on the factors impacting on SDS surgical outcome[60], utilizes six factors predicting complete cytoreduction: FIGO stage (I/II vs. III/IV), residual disease after primary cytoreduction (0 mm vs. >0 mm), PFS (<16 months vs. ≥16 months), ECOG performance status (0-1 vs. 2-3), CA125 (≤ 105 vs. > 105 U/ml) and ascites at recurrence (absent vs. present). Memorial Sloan Kettering criteria are also used to predict for complete gross resection in secondary cytoreductive surgery in EOC[61].

If there is no surgical option, systemic therapy is used to control the disease as long as possible. Several clinical trials have changed the landscape of care and remain an active area of investigation to overcome resistance. The type of treatment will be based on patient, time of recurrence, tumor histology and disease biology. Given that high grade serous ovarian cancer (HGSOC) is the most common type of EOC, we will focus on this specific group. The other histology subtypes including low grade serous, clear cell, endometrioid and mucinous are described in the supplementary (**Supplementary**).

High Grade Serous Ovarian Cancer (HGSOC)

Epidemiology/Origin

HGSOC is the most common type accounting for 75% of all EOC. The contemporary portrait of HGSOC pathogenesis has evolved from the notion that it develops from the ovarian epithelium to the epithelium of the distal fallopian tube[62]. Serous tubal intra epithelial carcinomas (STIC) are suspected to be the precursor lesion of some HGSOC, with molecular features involving mutations in *TP53* as an early event[63]. Bilateral salpingo oophorectomy is the standard of care for risk-reduction in *BRCA1/2* carriers. Prevention studies are currently assessing bilateral salpingectomy with delayed oophorectomy in women with high risk[64].

Hereditary susceptibility

As 15-20% of HGSOC have germline *BRCA1/2* mutations, diagnosis should trigger genetic testing[65]. The confirmation of germline mutation in a patient should also lead to offering germline testing offered to the in first degree relatives to identify carriers who may benefit from screening. In family predisposition studies, the cumulative risks of EOC by the age of 80 are estimated to be 44% in *BRCA1* and 17% in *BRCA2* mutation carriers[66]. Female *BRCA1/2* carriers should consider prophylactic risk reduction surgery after childbearing and around age 38, when the risk of EOC begins to increase as this is currently the only proven risk-reducing strategy[67]. Other genes of moderate penetrance involve *RAD51C, RAD51D* and *BRIP1*; although their individual mutation frequency is uncommon (<1% each), cumulatively they may be responsible for ~5% of EOC. Therefore, a genetic-testing for women with HGSOC includes *BRCA1/2* and other susceptibility genes[68]. Current studies are also evaluating early detection of *TP53* in blood or uterine lavage as a potential genomic screen[69,70].

Pathology

The growth pattern of HGSOC is heterogeneous, involving large papillae, being glandular, solid and occasionally micropapillary with frequent necrosis; it is defined by its high grade nuclei and mitotic index[71] (**Figure 2**). Immunohistochemistry (IHC) stain is abnormal for p53, diffusely expressed for p16 and elevated for Ki67; additional markers include ER, PR, WT-1 and PAX8.

Molecular abnormality

HGSOC is characterised by ubiquitous inactivating mutations in *TP53*[71], high-frequency somatic copy number alterations (CNAs), and whole genome duplications[72]. HGSOC are associated with lower prevalence but recurrent somatic mutations in *NF1*, *BRCA1/2*, *RB1* and *CDK12*[72] in around 5-8% of tumours (**Figure 3**). HGSOC is also characterized with frequent DNA gains and losses, making this cancer chromosomally unstable, with potential for acquired chemoresistance (*CCNE1* amplification)[73]. Heterozygous and homozygous loss is an important mechanism for inactivation of tumour suppressors[74]. Genomic analyses demonstrate HR is defective in nearly half of HGSOC[72]. This HR deficiency (HRD) is a key determinant of platinum sensitivity in HGSOC and has been exploited for treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[75]. Myriad HRD test and Foundation Medicine loss-of-heterozygosity (LOH) assay assess HRD in tumours as a potential predictive biomarker for PARPi therapy. Molecularly, HGSOC may be stratified into four different prognostic subtypes (C1/mesenchymal, C2/immune, C4/differentiated and C5/proliferative)[72,76,77] and potentially seven copy-number signatures[78]; both stratification methods require prospective validation to be used in a predictive way.

Treatment

In the platinum-sensitive recurrence setting, if surgery is not indicated, a re-challenge with platinum doublet chemotherapy is standard, with 6-8 cycles of therapy[79-82]. Maintenance strategies have been developed to delay subsequent progression and possibly improve OS[83]. Phase III trials with bevacizumab showed a significant benefit for maintenance on disease control rate[84,85]. In the OCEANS trial, the addition of bevacizumab to carboplatin/gemcitabine increased median PFS from 8.4 and 12.4 months (HR 0.484; 95% CI, 0.388-0.605; log-rank p<0.0001). GOG213 confirmed the benefit of adding

bevacizumab to carboplatin and paclitaxel with improvement in OS after correcting for PFI (HR of 0.823; 95% CI, 0.680-0.996; p=0.0447)[85].

A re-challenge with chemotherapy plus bevacizumab for platinum-sensitive recurrence and patients who previously received bevacizumab as first line showed a clinical benefit with a median PFS from 8.8 to 11.8 months without and with bevacizumab, respectively (HR 0.51, 95% CI, 0.41-0.64, p<0.001) but no significant difference in OS[86]. The benefit of adding and continuing an anti-angiogenic agent was further confirmed with cediranib[87].

PARPi have been successfully implemented in recurrent HGSOC by leveraging inherent defects in DNA repair mechanisms present in around 50% of HGSOC due to mutations in *BRCA1/2* or associated HRD genes, or functional inactivation through methylation[72]. PARPi have shown remarkable activity as single agent in women with recurrent disease regardless of *BRCA1/2* mutation, with improved activity in women with *BRCA1/2* mutation and platinum-sensitive disease[88-91]. Olaparib was the first PARPi approved initially for the treatment of advanced EOC in patients carrying germline *BRCA1/2* mutations who have received three or more previous lines of chemotherapy with response rate of 31.1% (95% CI, 24.6-38.1)[89,92]. In December 2016, the USA Food & Drug Administration (FDA) granted accelerated approval of rucaparib for the treatment of patients with HGSOC carrying deleterious germline or somatic *BRCA1/2* mutations previously treated with two or more lines of chemotherapy[90,93] based on the investigator-assessed objective response rate of 54% [95% CI, 44-64], and median duration of response of 9.2 months (95% CI, 6.6-11.7). Olaparib was approved in Europe as maintenance treatment in patients with platinum-sensitive relapsed HGSOC characterized by *BRCA1/2* mutations[94]. Among patients with a *BRCA1/2* mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11.2 months [95% CI, 8.3-not calculable] *vs* 4.3 months [3.0-5.4]; HR 0.18 [0.10-0.31]; p<0.0001); for patients with wildtype *BRCA1/2*, the difference was lower (7.4 months [5.5-10.3] vs 5.5 months [3.7-5.6]; HR 0.54 [0.34-0.85]; p=0.0075)[95]. In women with *BRCA1/2* mutations, SOLO2 trial confirmed the significance of maintenance, which was followed by FDA's approval of olaparib as maintenance therapy in women with platinum-sensitive disease following response to chemotherapy[96].

The benefit of maintenance PARPi extends beyond *BRCA1/2* mutation and HRD. Following the results of the phase III NOVA study, niraparib received FDA approval as maintenance treatment of patients with platinum-sensitive recurrent EOC who have achieved a complete or partial response following platinum-based chemotherapy regardless of *BRCA* status[97]. Patients treated with niraparib had a significantly longer median PFS than those treated with placebo, including 21.0 vs. 5.5 months in the germline *BRCA1/2* cohort (HR 0.27; 95% CI, 0.17-0.41), as compared with 12.9 vs. 3.8 months in the non-germline *BRCA1/2* cohort for patients who had tumours with HRD (HR 0.38; 95% CI, 0.24-0.59) and 9.3 vs. 3.9 months in the overall non-germline *BRCA1/2* cohort (HR 0.45; 95% CI, 0.34-0.61; p<0.001 for all three comparisons). The most recent addition to the pharmacopeia has been rucaparib, which demonstrated significant benefit for maintenance therapy following a good response to platinum-based chemotherapy following recurrence[98]. Median PFS in patients with a *BRCA*-mutant carcinoma was 16.6 months (95% CI, 13.4-22.9) in the rucaparib group versus 5.4 months (3.4-6.7) in the placebo group (HR 0.23 [95% CI, 0.16-0.34]; p<0·0001); in patients with a HRD carcinoma, it was 13.6 (10.9-16.2) versus 5.4 months (5.1-5.6; 0.32 [0.24-0.42]; p<0.0001).

Collectively, the greatest benefit of PARPi as single agent therapy has been observed in women with HGSOC containing deleterious germline or somatic mutations in *BRCA1*/2[99], followed by women

with evidence of HRD; however, biomarkers have not been specific enough to predict benefit. Novel strategies are underway to avoid the use of chemotherapy and involve combination of targeting drugs, such as olaparib/cediranib[100]; regardless *BRCA1/2* status at the time of platinum-sensitive relapse.

Recurrent disease follows a frequent relapse-response pattern before becoming resistant to treatment. For platinum-resistant disease, various sequential mono-chemotherapies including weekly paclitaxel, liposomal doxorubicin and gemcitabine are used until subsequent progression or unacceptable toxicity. However, as the expected response rate in the platinum-resistant setting are low (~10-15%), several trials are investigating new agents to overcome resistance[101]. In the platinum-resistant setting, a phase III trial (AURELIA) showed that adding bevacizumab to various chemotherapy regimens increased the PFS from 3.4 to 6.7 months (HR 0.48 95% CI, 0.38-0.60; unstratified log-rank p<0.001). An unplanned exploratory subgroup analysis reported that the PFS benefit was greatest in the weekly paclitaxel arm, with an improvement from 3.9 to 10.4 months upon addition of bevacizumab[102].

Patients with refractory disease, defined as progression during the first line of platinum-based chemotherapy, have a very poor prognosis with very low response rate to standard chemotherapy. Unfortunately, these patients are often excluded from trials and there is an urgent need to define options for this group.

Future directions

After the approval of anti-angiogenics and PARPi, there is an active interest in combination therapy to overcome resistance. Acquired drug resistance mechanisms to PARPi involving *BRCA* mutation reversions and *ABCB1* fusions are well known but they are often not present in all tumour cells[103,104], suggesting that multiple resistance mechanisms may be present within an individual patient. Research aimed at delineating novel resistance mechanisms is needed. Another area of investigation is the immune infiltration and tumour hypoxia[105], and how modulating the microenvironment may prompt responses to therapy. Since preliminary results of immunotherapy as single agent showed low response rates in HGSOC[106], novel approaches are based on combination strategy and T-cell therapy[107].

Efforts are also ongoing in improving drug delivery; antibody-drug conjugates (ADCs) are an important class of highly potent biopharmaceutical drugs designed as a targeted therapy. ADCs consist of an antibody designed against a specific target linked to a cytotoxic agent[108]. Because targets do not have to be drivers of tumour growth, ADCs are an emerging class of therapeutics, particularly in OC lacking clear oncogenic drivers. As an example, Mirvetuximab soravtansine (IMGN853) consists of a humanized anti-folate receptor (FR) monoclonal antibody attached to the cytotoxic maytansinoid, DM4[109]. This is currently being assessed in phase III trial for patients with FR-positive platinum-resistant EOC. The ADC strategy offers the possibility to investigate the interest of functional imaging based on the identification of the target and tissue analysis[110].

The current challenge is to define the appropriate combination/sequence strategy for a patient at a specific time and then identify mechanisms of resistance that will guide the treatment individualized to each patient.

Patient journey: Evolution of disease

In HGSOC, *TP53* mutation is followed by multiple sequential mutational processes that drive the pathogenesis into a highly complex, genomically unstable tumour with low frequency of oncogenic mutations and few recurrent copy number alterations[111]. These aberrations can evolve with time and exposure to different lines of treatment, increasing the risk of developing therapeutic resistance. Majority of targetable mutations are concordant over time, despite inter-current chemotherapy and associated clonal selection[112]. However, reversion mutations restoring the open reading frame of *BRCA* have been described with PARPi treatment[113,114], as well as recovery of BRCA1/2 protein expression[115], which predict for resistance to therapy[116]. Whole genome sequencing has elegantly established the potency of the somatic genome, characterized with diverse DNA repair deficiencies that can be used to stratify ovarian cancers into distinct biological groups with predictive signatures of resistance or relapse[117]. Next-generation sequencing (NGS) is further facilitating deeper understanding of resistance and response; in particular, the analysis of exceptional responders in clinical practice allows for discovery of predictive signatures that may revitalize or reposition the use of targeted agents[118]. Unique genomic determinants may be associated with the exceptional outcome in HGSOC patients; concurrent HR deficiency and RB1 loss were associated with favorable outcomes, suggesting that co-occurrence of specific mutations might mediate durable responses[119].

Spatial and temporal intra-tumour heterogeneity is a major challenge for the development of precision medicine and treatment[120-122]. Several new targets have been identified for each tumour type and are under evaluation as part of clinical trials (**Figures 2-4**). Given the complexity involved in the mechanisms of therapeutic resistance, the characterization of the disease processes at recurrence is key to identify the best treatment strategy for a patient at that time (**Figure 5**). Combination therapy targeting DNA damage response, cell-cycle, signaling pathway and tumour microenvironment may be required to control the profound genomic complexity of evolution of OC. This involves a change in practice and a need for sequential biopsy, or liquid biopsy, to define the mechanism of resistance involved in the current episode of recurrence. Recent studies have shown the feasibility to detect reversions mutations in circulating tumour DNA (ctDNA) upon resistance to therapy, suggesting its potential clinical utility[114,123]. Circulating tumour cell collection has demonstrated “real-time” molecular characterization of drug-response at multiple time points in some cancers[124].

The cellular, molecular and spatial heterogeneity of ovarian cancer has led to very active consideration of harnessing the immune system to target this disease (Figure 6). Tumour infiltrating lymphocytes (TILs) are associated with improved clinical outcome in EOC patients[125-127]; prognostic subtypes have also been suggested[74,128]. Early studies have incorporated interventions with immune checkpoint blockade, cancer vaccines, and adoptive cell therapy. Initial trials included all subtypes of EOC, and response rates appear to be modest with checkpoint inhibitors as single agent in HGSOC with some encouraging activity seen in CCOC[129-132]. Beyond the PD-1 and CTLA-4 pathways, additional tolerogenic mechanisms can be targeted and used in combination with immune therapies, such as chemotherapy or anti-angiogenics. The hypothesis that combination with chemotherapy or targeted agents will improve immune exposure and activity of EOC has very quickly led to many combinations and randomized clinical trials in recurrent and first line setting.

Quality of life – Symptom management

Given the potential chronicity of EOC, patients may experience a multitude of relapses and treatment-related adverse events (AE) that can impact quality of life (QOL). Efforts are on-going to integrate this endpoint into clinical trials and design studies in recurrent disease where the patient reported outcomes (PRO) are major endpoints[133]. At the time of recurrence, the goal of treatment is to control the disease and maintain QOL. This means that treatments have to ensure an acceptable safety profile and balance symptom benefit with risks, particularly in the platinum-resistant setting[134]. To incorporate a patient's perspective on side effects, PRO have been integrated into standard reporting of AE based on Common Terminology Criteria for Adverse Events (CTCAE) as PRO-CTCAE[135,136].

Malignant bowel obstruction (MBO) is the most common complication of EOC progression and is described by patients as the most devastating event experienced over their disease trajectory with a median survival of <5 months[137]. This is a major clinical challenge due to limiting therapeutic options associated with substantial symptoms, such as the inability to maintain oral intake, vomiting and abdominal pain, which lead to nutrient deprivation. MBO management is not well defined and includes potential surgical or radiology intervention, medical support and the ethical dilemma of total parenteral nutrition (TPN). Efforts are on-going to offer a multidisciplinary management including surgery, chemotherapy, radiation, interventional radiology and include patients' preferences[138,139]. In this setting, the question of TPN remains difficult as the selection of patients who will benefit from TPN is not well described and the majority of patients will die from cancer process, not starvation[140]. Early intervention of palliative care is also important to improve patient care[141,142].

Conclusion

The efforts on understanding and characterizing the different types of EOC have been leveraged into new therapies, transitioning to standard of care. Discovery research is advancing into elegant hypothesis driven trials and translational research.

Access to clinical trials and international collaboration has been crucial in this progress, particularly for the rare tumours types. Building strong multidisciplinary network with integration of discovery research with clinical practice is key to improve precision medicine that will impact patient care. The delivery of value-based and patient-centered care is central to improving outcomes as is learning from each patient, from the exceptional responders to the refractory patients. The value of cancer treatment is based on clinical benefit, toxicity, and improvements in patient symptoms or QOL in the context of cost[143]. Patient engagement and input should be integrated to make these efforts meaningful and measurable.

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Statement of contributions

Stephanie Lheureux: writing of the summary, introduction, HGSOC section, future direction, disease evolution, patient management and overview and revision of all the manuscript

Charlie Gourley: writing of the rare histology subtype section of EOC, overview of all the manuscript and expertise on the direction, management of ovarian cancer

Ignace Vergote: Writing of the surgical management of EOC and overview of all the manuscript

Amit Oza: Seminar design and overview, scientific expertise, guidance and support in the manuscript writing, review of all the data and overview of the entire manuscript

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LEGENDS

Figure 1: **Evolving management strategies based on disease biology and molecular profiling of novel biospecimens.** Integrated approach combining understanding of ovarian cancer disease biology and evolution, application of novel omics-based technologies as a part of research based studies or clinical trials.

Figure 2: Different histological subtypes of epithelial ovarian cancers and their salient features. HGOSC stands for High grade ovarian serous cancer; LGOSC stands for Low grade ovarian serous cancer. P53 and WT1 staining in HGOSC is shown. The magnifications for H & E pictures range between 50-400x, whereas, IHC is 50x.

Figure 3: **Common molecular abnormalities in ovarian cancer**. The pie chart on the left demonstrates the breakdown of epithelial ovarian cancer according to histological subtype. The pie chart on the right shows the breakdown of the main molecular abnormalities that are felt to drive high grade serous ovarian tumours (*P53* mutation is an almost ubiquitous finding). EMSY: EMSY, BRCA2 Interacting Transcriptional Repressor

Figure 4: **Different molecular targets and pathways in ovarian cancers currently developed or under investigation.** The molecular targets may arise from within a cancer cell or from the tumour microenvironment, such as host immune cells or vascular tissue.

Figure 5: Disease evolution and treatment options in ovarian cancer. Combination therapy targeting DNA damage response, cell-cycle, signaling pathway and tumour microenvironment may be required to control the profound genomic complexity of evolution of HGSOC. Bevacizumab: vascular endothelial growth factor (VEGF) inhibitor. Olaparib, niraparib, rucaparib: Poly (ADP-ribose) polymerase (PARP) inhibitors. SDS: secondary debulking surgery. M: maintenance. T: therapy. TBD: to be determined. Vertical red lines: time of recurrence.

Figure 6: Different Immunotherapeutic strategies in targeting ovarian cancers. This ranges from targeting the ovarian cancer cells, the tumour microenvironment or boosting the host immune system.

Table 1. Leuven and Essen criteria for considering neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) in FIGO stage IIIC and IV ovarian carcinoma. Adapted from Vergote *et al*[144].

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Low grade serous ovarian cancer (LGSOC)

Epidemiology

The most up to date information regarding LGSOC demographics comes from retrospective analysis of 350 patients from the MD Anderson LGSOC longitudinal database[1]. The median age of diagnosis was 46 years and 96% of patients presented with disease spread beyond the pelvis. The median PFS (28 months) and OS (102 months) were well in excess of what would be expected for HGSOC but due to the younger age at diagnosis (median 10-15 years younger than HGSOC), LGSOC still accounts for a considerable number of life years lost. Multivariate analysis of this dataset also demonstrated superior outcome for patients aged >35 years at diagnosis (HR=0.53, p<0.001) and those with no disease evident at the end of primary surgery (HR=0.56, p<0.001)[1].

Genetics/molecular biology

LGSOC is characterised by frequent activation of MAPK pathway, which might associate with superior survival[2]. *KRAS* is the most frequently mutated gene (19-35%)[3-6] followed by *BRAF* (2-33%)[3-6] and *NRAS* (22%)[3]. *BRAF* mutations might be more frequently associated with serous borderline tumours or early stage LGSOC, and under-represented in late stage or relapsed disease[5]. Additional genetic abnormalities in LGSOC include mutations in *NF1*, *EIFIAX*, *USP9X* and *FFAR1* genes[3,7]; *TP53* mutations are very rare. Interestingly, growing evidence suggests the importance of endocrine therapy in LGSOC; in a series of 26 LGSOC, ER (oestrogen receptor) was expressed in 81%, PR (progesterone receptor) in 35%, AR (androgen receptor) in 54%, LHR (lutenizing hormone receptor) in 65%, GnRHR (gonadotropin hormone releasing hormone) in 100% of cases[8].

Non-genetic risk susceptibility

Serous borderline tumours are identified in association with 60% of LGSOC[9] but the actual percentage of serous borderline tumours that subsequently relapse as LGSOC needs to be confirmed; studies have reported the rate to be as low as 2%[10].

Diagnosis

In 2004, Malpica *et al* described a two-tier system for grading serous ovarian cancer that is based on nuclear atypia and mitotic rate, as opposed to the previously used three-tier FIGO system[9]. These patients had co-existent serous borderline tumours in 60% of cases[9]. Clarification of the molecular biology and discrete clinical behaviour confirms that this dichotomisation successfully distinguishes LGSOC and HGSOC as separate clinical entities. In young patients, germ cell tumours are included in the differential diagnosis; this includes assessment of serum LDH, AFP, β-HCG as well as inhibin and CA125.

Treatment

Primary resection to zero macroscopic residual disease is associated with superior PFS and OS[1]. Given the relative chemo-resistance of LGSOC, complete surgical resection is the primary treatment of choice; neoadjuvant chemotherapy is not recommended. The radiological response rate to NACT was 4% and although a further 88% achieved stable disease, the latter figure may reflect innate disease

biology rather than chemosensitivity[11]. In young patients, consideration of fertility issues (and pre-surgical counselling) is important. A recent large retrospective study has suggested that first-line maintenance therapy with hormonal agents significantly extends PFS in stage II to IV LGSOC[12]. Median PFS for the observation group was 26.4 months (95% CI, 21.8-31.0), compared with 64.9 months (95% CI, 43.5-86.3) for the hormonotherapy group (p<0.001); OS was not significantly different (102.7 vs. 115.7 months; p=0.42). These data have led to calls for a prospective randomised study to identify the optimal first line systemic treatment strategy.

In the relapsed disease setting, the response rate to chemotherapy was low ~4%[13] and hormonal treatment can be a reasonable option. SDS appears to be a valid strategy if complete resection can be achieved. In a retrospective review of 41 LGSOC cases, patients with no gross macroscopic residual had a median PFS of 60 months vs. 11 months for patients with gross residual (p=0.008) and a median OS of 167 months vs. 89 months (p=0.1)[14]. In addition, MEK inhibition is also actively explored. A phase II study of selumetinib demonstrated a 15% response rate in heavily pre-treated patients[15] whereas the results from randomised studies on other MEK inhibitor are pending. Although *BRAF* mutations are fairly rare in relapsed or persistent LGSOC, there are case reports of impressive efficacy of BRAF inhibitors in specific cases of V600E mutations[16,17]. A retrospective single institution study of 40 patients who received bevacizumab (mostly in combination with chemotherapy) reported a 47% response rate with a further 30% disease stabilisation rate[18]. Given the low response to chemotherapy in LGSOC, it is likely that much of this efficacy is contributed to bevacizumab.

Focus areas for future research

The optimal first line treatment still remains to be defined. Hormone therapy may be important, but a randomised first line study is required to answer this question. The role of MEK inhibition remains to be defined, as does the role of biomarkers for selecting patients for MEK inhibition. The molecular features of LGSOC cases without MAPK activation also remain to be described.

Clear cell ovarian cancer (CCOC)

Epidemiology

The median age of diagnosis of CCOC is 55 years[19]. CCOC makes up 5-12% of all EOC in North American populations[19,20] but 24% and 19% in the Japanese and Taiwanese cohorts, respectively[21,22]. In Japan, Taiwan and Korea there is a steady rise in incidence of CCOC that has not yet peaked[19,22,23]. The reason for the geographical or racial difference in incidence is not clear but Japanese-Americans with CCOC comprise 9% of EOC diagnoses in USA, compared to 3% in whites and Hispanics[24], suggesting that both environmental and genetic factors impact on CCOC incidence. In the context of the disease stage, in North American populations CCOC makes up 26% of all early (stage I/II) disease compared to 5% of all advanced (stage III/IV) disease[20], in contrast to HGSOC that makes up 36% of all early stage and 88% of all advanced stage disease[20].

Early stage CCOC has a better prognosis than early stage serous ovarian cancer[25,26]; however, in the advanced stage setting, the prognosis of CCOC is worse[26,27] likely due to its high level of inherent chemotherapy resistance. Patients with relapsed CCOC have a significantly inferior post-relapse survival compared to patients with relapsed serous ovarian cancer (HR =2.35; p<0.0001)[28].

Genetics/molecular biology

The only common familial syndrome associated with the development of clear cell ovarian cancer is Lynch syndrome; a systematic review suggested that ovarian cancer patients with Lynch syndrome had a predominance of endometrioid and clear cell histology[29]. This was confirmed in a recent exome-sequencing study in which cases of hypermutated CCOC genomes were associated with germline or somatic MMR gene mutations[30]. 20% of patients with clear cell or endometrioid ovarian cancer have loss of mismatch repair (MMR) protein expression[31]. Approximately two thirds of these loss events are due to germline mutation in one of the four main MMR genes (MLH1, MSH2, MSH6 or PMS2). On the basis that cancers with MMR gene deficiency have a high chance of responding to immune checkpoint inhibition this is currently being tested in prospective clinical trials in these histological subtype[32].

The molecular basis for the link between endometriosis and both clear cell and EOC was made in a pivotal study which sequenced whole transcriptomes from 18 CCOCs and found somatic mutations in the *ARID1A* gene in six of the samples[33]; this was later validated in a much larger tissue set. They also identified *ARID1A* mutations and loss of BAF250a (the protein product of ARID1A) in tumour and adjacent areas of endometriosis but not in distant endometriotic lesions, providing evidence of cause and effect. *ARID1B* and *SMARCA4,* involved in the chromatin remodelling process, have also been implicated in CCOC. Other molecular abnormalities associated with CCOC are mutational activation of the PI3K/AKT and MAPK pathways (Figure 3)[30,34]; interestingly, patients with activating mutations of either the PI3K/AKT or MAPK pathway might have better prognosis than patients without these mutations[34].

Non-genetic risk susceptibility

In a very large study comprising 13,226 controls and 7,911 women with invasive ovarian cancer, self-reported endometriosis was associated with a significantly increased risk of clear cell (odds ratio, OR, 3.0, $p<0.0001$), low grade serous (OR 2.1, $p<0.0001$) and endometrioid (OR 2.0, $p<0.0001$) ovarian cancer[35]. No association with HGSOC or mucinous ovarian cancer was identified. In a small retrospective study comparing CCOC arising in endometriosis to CCOC not arising in endometriosis, the endometriosis-associated patients were younger, have unilateral tumours and less likely to have ascites[36].

Diagnosis

CCOC usually presents with an isolated pelvic mass (bilaterality occurring in around 2%)[37] and 55% of CCOC present with stage 1 disease[27]. Cross-sectional imaging with CT or MRI scan is a pre-operative requisite; CCOC is the most likely histotype to have a poor uptake of fluorodeoxyglucose in positron emission tomography[38]. Expert pathological diagnosis is crucial since HGSOC with clear cell change can often be mistaken for bona fide CCOC[39].

Treatment

Given the relative chemo-resistance of CCOC, complete surgical resection is the primary treatment of choice; neoadjuvant chemotherapy is not recommended. Data from the MITO-9 study suggested that lymphadenectomy improved disease-free and OS in Italian CCOC patients[40]. This benefit

may be due to stage shift, although clearly the inclusion of lymphadenectomy is beneficial in terms of providing the most accurate staging information. Many guidelines recommend use of adjuvant chemotherapy for all stages of CCOC but retrospective subgroup analyses of the pivotal ACTION study of chemotherapy in early stage ovarian cancer as well as subsequent retrospective cohort analyses casted doubt on the impact of chemotherapy in CCOC since early stage CCOC patients had no significant disease free survival benefit from use of adjuvant chemotherapy (63 patients; p=0.4). In contrast, early stage serous ovarian cancer patients did derive disease free survival benefit from adjuvant chemotherapy (156 patients; p=0.01)[37]. In a retrospective analysis of 1,995 stage I CCOC patients from the Surveillance, Epidemiology, and End Results (SEER) database, no benefit for adjuvant chemotherapy was identified at any substage of disease, although this result could have been affected by selection bias as chemotherapy was more likely to have been used in patients with higher disease sub-stage[41].

In the setting of advanced (stage III/IV) CCOC, a retrospective analysis performed by the Hellenic Cooperative Oncology Group showed a response rate of 45% to first-line platinum-based chemotherapy compared to an 81% response rate in serous ovarian cancer[42]. This is likely an overestimate of CCOC chemosensitivity because some of these tumours may be HGSOC disguised as CCOC[39,43]. In a later retrospective study that had the advantage of formal central pathology review, the response rate to chemotherapy was 32% compared to 78% in serous ovarian cancers[27]. In an attempt to improve the efficacy of first line chemotherapy in CCOC, an international randomised phase III trial of irinotecan plus cisplatin versus carboplatin and paclitaxel was performed in 667 patients with stage I-IV disease but no significant benefit was demonstrated in the test arm[44]. In 72 patients with relapsed CCOC from the MITO-9 study, the response rate to platinum-based chemotherapy was a surprising 80% in patients with a PFI >6 months[45]. The response rate to non-platinum chemotherapy in platinum-resistant patients was 33%, although a high response rate (8/12 patients; 66%) was seen with gemcitabine[45].

Given the molecular similarities between CCOC and clear cell renal carcinoma, sunitinib has been used in advanced CCOC with some efficacy[46,47]; results from the recent GOG254 study are pending. While ovarian cancer immunotherapy has largely failed to deliver the results seen in other cancers, success has been observed in CCOC patients[48,49], potentially due to MMR deficiency that is known to confer high mutational load and sensitivity to immune checkpoint blockade[32]. Radiotherapy had no benefit for patients with stage IA, IB or IC (rupture alone) patients, but in other stage IC and stage II patients, it improved 5-year disease-free survival by 20%[50].

Focus areas for future research

Considerable uncertainty still exists regarding the extent of benefit and optimal chemotherapy in the first line early stage, first line late stage and relapsed disease settings. It may be that immune checkpoint inhibitors and small molecules targeting specific intracellular pathways will be more successful. Clarifying these matters will require international clinical trials with very rigorous pathology review and confirmation by molecular profiling in order to ensure that only bona fide CCOC are included.

Endometrioid Ovarian Cancer

Epidemiology

Endometrioid ovarian cancer is the second most common type of EOC. Synchronous diagnosis of endometrioid cancers in the uterus at same time as diagnosis of ovarian cancer is well described[51] and may occur in about 5% of newly diagnosed EOC[52]. Whole genome sequencing has identified a common ancestry of synchronous ovarian and endometrial cancer and late development of peritoneal carcinoma from the same ancestry clone after a period with established endometriosis[53]. Epidemiologic studies suggest that endometrioid and clear cell ovarian cancers arise from the endometrium[54] with demonstrated differences in cell linage: endometrioid carcinomas seem to arise from the cells of the secretory cell lineage, whereas clear cell carcinomas arise from the ciliated cell lineage[55].

Molecular Biology

High grade endometrioid OC (HGEOC) shares some clinical and biological features of HGSOC with *TP53* gene abnormalities. Low grade endometrioid OC (LGEOC) showed mutations in *PI3KCA*, *BRAF*, and *KRAS* are prevalent.

Treatment

At initial diagnosis, there has been a consideration for performing surgery as the only intervention in women with well-differentiated or moderately-differentiated stage IA or IB disease. Surgery has to include full staging with hysterectomy, bilateral salpingo-oophorectomy, and omentectomy with assessment of undersurface of the diaphragm. Additionally, collection of biopsies of the pelvic and abdominal peritoneum and the pelvic and para-aortic lymph nodes, as well as peritoneal washings, should be performed[56-58]. For HGEOC, the treatment choices are similar to HGSOC, as these are both high-grade cancers, characterized by initial chemosensitivity with subsequent acquisition of increasing resistance at each recurrence. LGEOC shows more indolent behavior and retrospective studies describe low response rates to cytotoxic and hormonal agents.

Mucinous ovarian cancer

Mucinous ovarian cancers are most commonly diagnosed at an early stage. Differentiation between primary and metastatic involvement of the ovary is critical for optimal patient management[59]. The incidence of true advanced ovarian mucinous tumours has reduced due to the systematic use of systemic IHC for the cytokeratins CK7 and CK20, which help to distinguish ovarian from the more common gastrointestinal source of these cancers. The percentage of ovarian carcinomas represented by primary mucinous tumours is ~ 2.4%[60]. This rare type of cancer has nearly 100% *KRAS* mutation and a high frequency of HER2 amplification[1]. Given that this tumour is often chemoresistant, upfront surgery is the cornerstone of the treatment; the value of adjuvant chemotherapy is unclear. The poor response to chemotherapy is most notably seen in advanced or recurrent disease where there is a need to develop systemic treatments[61].

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Fast Facts

Ovarian cancer – Lancet Oncology

- Ovarian cancer consists of a number of diseases: high grade serous, low grade serous, clear cell, mucinous and endometrioid ovarian cancer; each subtype is associated with distinct precursor lesions, tissues of origin, molecular biology, clinical presentation, chemosensitivity and patient outcome. As such, treatment decisions are no longer based on staging of the disease, but on histology type and an array of its features that are most likely to contribute to drug response in the absence of definitive predictive markers.
- Majority of ovarian cancers develop sporadically, but approximately 10-15% are hereditary. Within the hereditary group, 65-75% of cases are caused by inactivating *BRCA1/2* gene mutations, whereas 10-15% of cases have been found to be are associated Lynch syndrome.
- Diagnosis is hampered by non-specific symptoms and as such, majority of patients are diagnosed with late presentation of the disease. Disease staging is surgical and additional investigations include the measurement of CA125 concentrations and imaging.
- As clinical studies were predominantly conducted on the common subtype (high grade serous), evidence base established by landmark studies for treatment of ovarian cancer mainly relate to this particular subtype. Clinical trials need to be conducted on subtypes that are rare, such as clear cell, low grade serous, mucinous and endometrioid ovarian caner, in order to establish a subtype-specific standard of care.
- First line therapy includes primary debulking surgery with the goal of no residual disease, followed by 6 cycles of platinum based chemotherapy. High-grade serous and endometrioid ovarian cancer are initially chemosensitive, compared to relative chemoresistance of low grade serous, clear cell and mucinous ovarian cancers.
- Improvements have been demonstrated with targeted agents. In advanced stage with residual disease after primary debulking surgery, the addition of anti-angiogenic agent bevacizumab to the first line chemotherapy has shown improvement in progression-free survival and overall survival.
- Recurrence is seen in 75% of women who present with advanced disease. This is often an incurable situation but with improved understanding of the biology, maintenance strategies have been developed to delay subsequent progression and possibly improve overall survival. In this setting, bevacizumab and PARP (poly (ADP-ribose) polymerase) inhibitors (olaparib, niraparib, rucaparib) have been remarkably effective in controlling the disease.
- The road to understanding the mechanisms of drug resistance is still a long one and it will involve a multi-dimensional approach investigating genomic, transcriptomic, proteomic, epigenetic and microenvironmental changes during ovarian cancer trajectory, as well as designing better clinical trials, to overcome drug resistance and improve outcomes.
- Clinical challenges remain during the end-of-life stage when patients develop malignant bowel obstruction and other complex issues that do not have well defined management approach. Early intervention of palliative care is also important to improve patient care and quality of life.

Understanding the Disease Biology

Diagnosis - Subtype of EOC

Stage / Grade of the disease

Time and type of initial treatment

Susceptibility / Risk factors

Biomarker discovery

Samples studied: Tumor, Blood, Normal tissue, ct-DNA/cf-DNA, body fluids

Omics-based profiling

I. DNA: WGS/WES sequencing targeted

II. RNA: Total RNA/ mRNA or targeted RNA Sequencing /microarrays

III. Small RNA and non-coding RNA Sequencing

IV. Epigenetics- Bi-sulphite sequencing/methylation arrays

V. Transcription factors/ other regulatory proteins- ChIP Sequencing

VI. Proteins- Mass-spectrometry/ Protein microarrays

Development of New treatment options

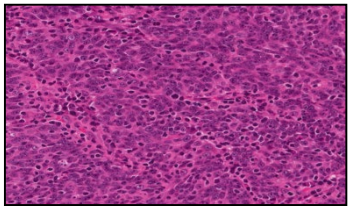
Integrating discovery of new biomarkers into

I. Research based studies

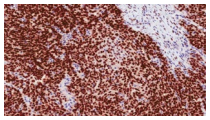
II. Clinical trials

III. Individualized medicine

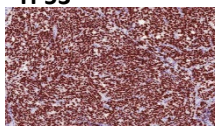
HGOSC



WT-1

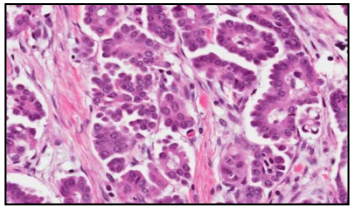


TP53



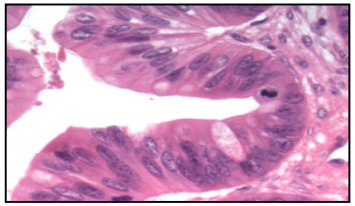
- Highly aggressive tumors
- Papillary or solid growth pattern
- Tumor cells with atypical, large irregular nuclei
- High proliferative rate
- Initial chemo-sensitivity with subsequent acquisition of increasing resistance
- Key targets: TP53, BRCA1/2, HRR genes

LGOSC



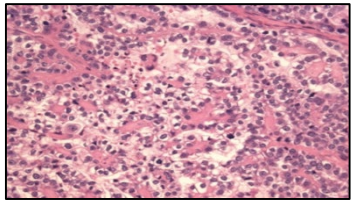
- Indolent behavior
- Micro-papillary pattern
- Tumor cells with small uniform nuclei
- Low proliferative rate
- Relative chemo-resistance
- Key targets: BRAF, KRAS, NRAS and PIK3CA

Mucinous



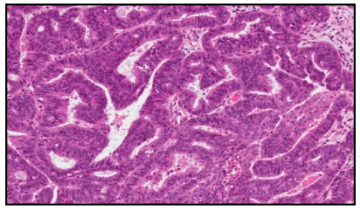
- Large size tumors filled with mucus like material
- Early stage diagnosis
- Chemo-resistant
- Key targets : KRAS, PIK3CA and HER2 amplification

Clear Cell

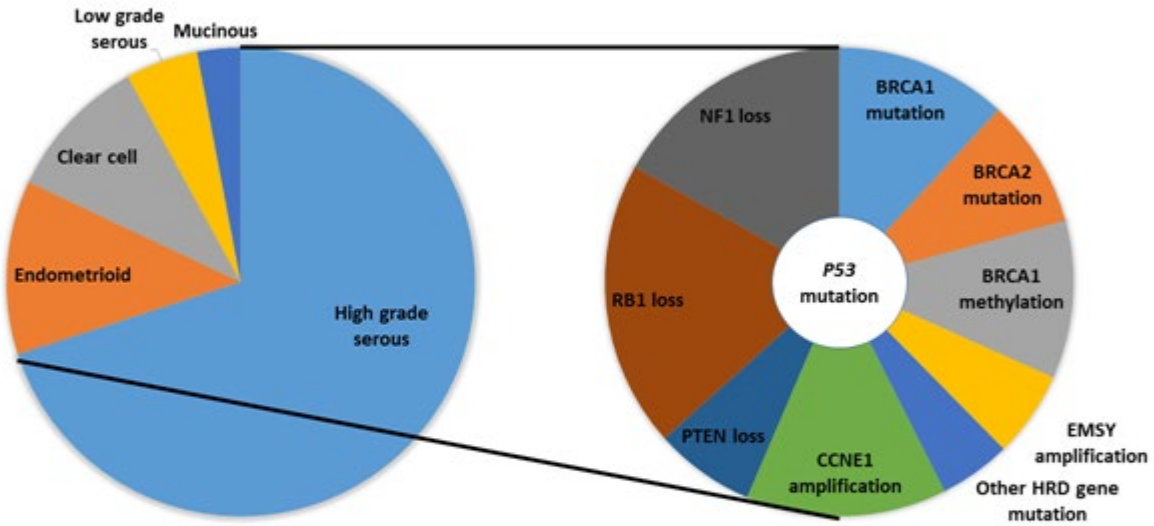


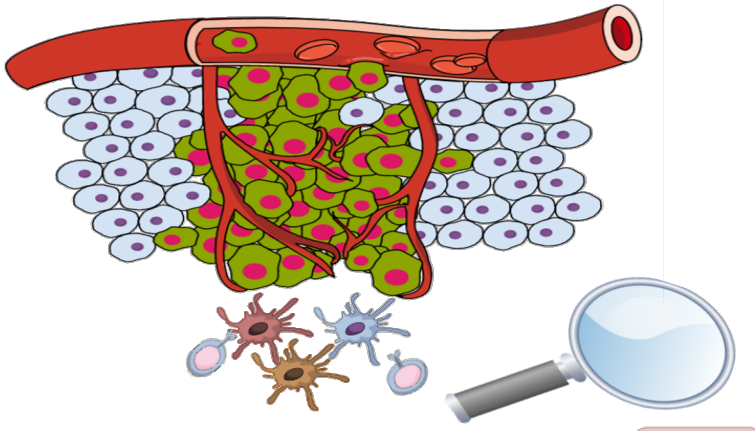
- Glycogen containing cells with clear cytoplasm
- Tubulo-cystic, papillary, solid or mixed patterns
- Frequently associated with endometriosis
- Early stage diagnosis
- Poor prognosis and resistance to chemotherapy
- Key targets: PIK3CA, ARID1A and PTEN

Endometrioid



- Solid and cystic patterns
- Frequently associated with endometriosis
- Low grade share the same profile as LGSOC
- High grade share similarity with HGSOC
- Key targets : PIK3CA, PTEN, ARID1A, POLE, MMR deficiency


Low grade serous
Mucinous
Clear cell
Endometrioid
High grade serous
NF1 loss
BRCA1 mutation
BRCA2 mutation
P53 mutation
BRCA1 methylation
RB1 loss
PTEN loss
CCNE1 amplification
EMSY amplification
Other HRD gene mutation



Microenvironment

Endothelial cells

Angiopoietin

PDGFR MET FGFR VEGFR1/2/3 Tie2 receptor

Anti- Angiogenics

Dendritic cell

CTL-A4

T-cell

Immune checkpoint inhibitors

PD1

PDL1

TCR

Survivin

MHC I

Survivac

Receptor inhibitors

GFR

Integrin

Hormonal therapy

FRα

ER PR

VEGF

Ras/Raf/ MEK

PI3K/AKT/ mTOR

Ras/Raf/MEK inhibitors

PI3K/AKT/ mTOR inhibitors

Cancer Cell

Microtubule targeting

Cell Cycle inhibitors

WEE1

M

G_2

G_1

S

TP53

CDK1/2

ATR

RNA PolII

DNA

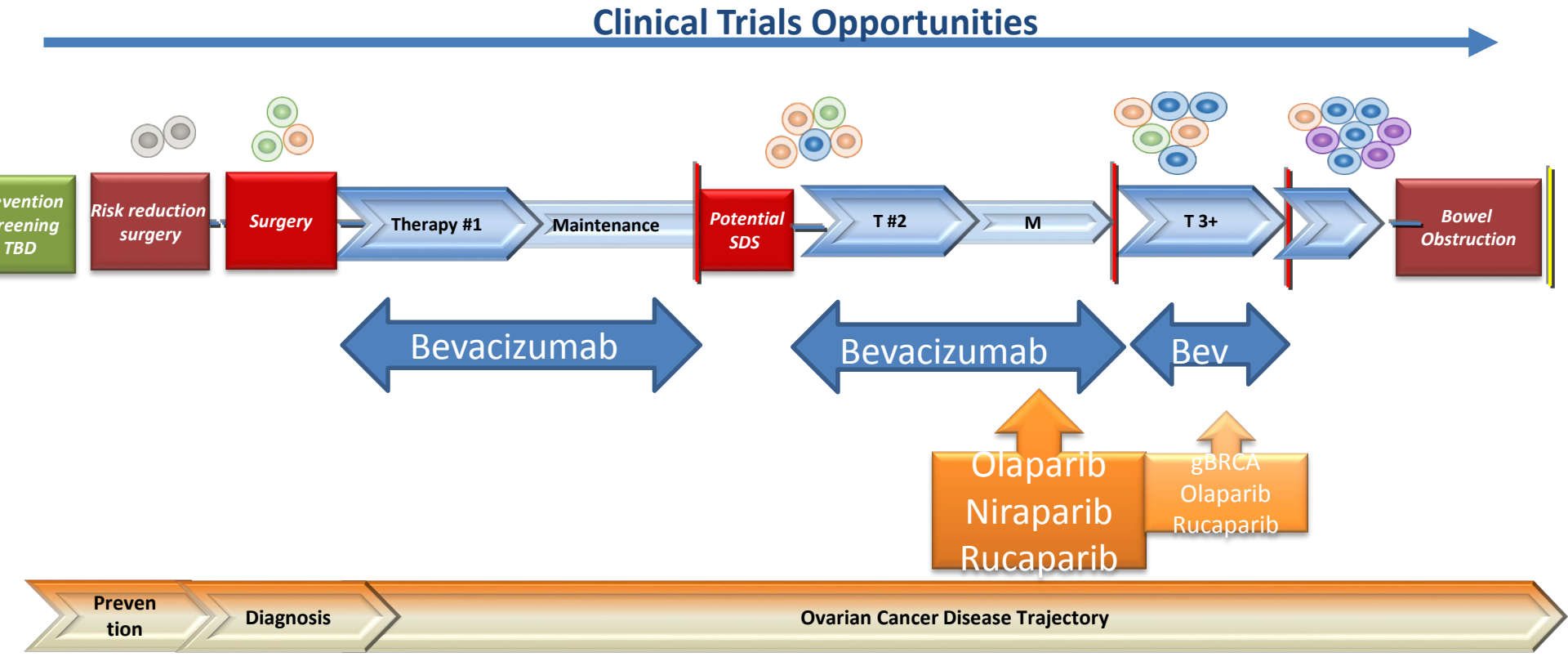
PARP

Alkylating agents

PARP inhibitors

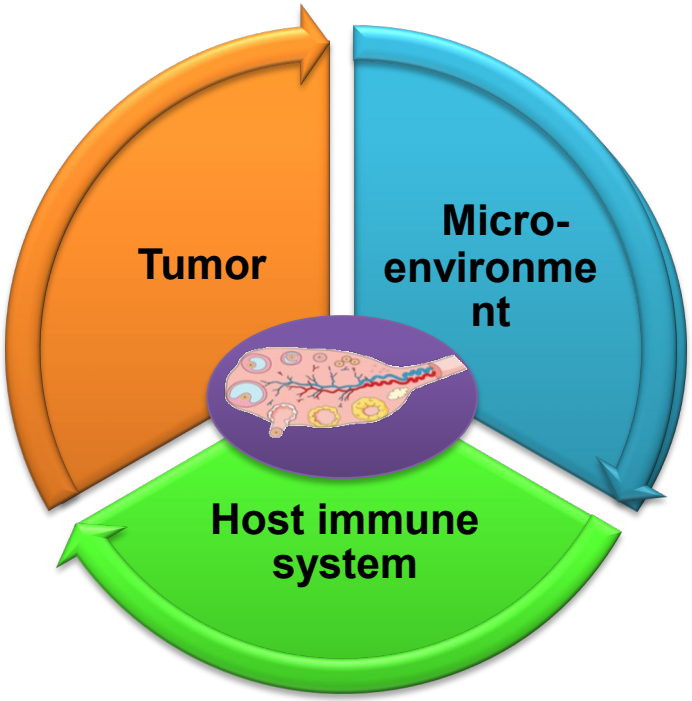
Nucleoside analogs

Topo II inhibitor


Clinical Trials Opportunities
vention
reening
TBD
Risk reduction surgery
Surgery
Therapy #1
Maintenance
Potential SDS
T #2
M
T 3+
Bowel Obstruction
Bevacizumab
Bevacizumab
Bev
Olaparib
Niraparib
Rucaparib
gBRCA
Olaparib
Rucaparib
Preven tion
Diagnosis
Ovarian Cancer Disease Trajectory

- Challenging the tumor mutation burden
- Targeting mutation neo-antigens
- Probing the biomarkers at DNA/RNA level that predict treatment response
- Adoptive cell therapy

- Immune-checkpoint blockades
- Anti-angiogenics
- Active tumor microenvironment
- Presence of tumor infiltrating cells
- Suppression of IDO expression



- Priming the immune cells with chemo- and radiotherapy
- Using cancer vaccines to generate potent effector T-cells
- Use of synthetic TCR or CAR modified T cells
- Replenishing the gut microbiome

Table 1. Leuven and Essen criteria for considering neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) in FIGO stage IIIC and IV ovarian carcinoma (Adapted from Vergote I., du Bois A., Amant F., Heitz F., Leunen K., Harter P. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? **Gynecol Oncol.** 2013;128(1):6-11)

Criteria	Essen criteria	Leuven criteria
diagnosis:	Biopsy with histologically proven epithelial ovarian (or tubal or peritoneal) cancer FIGO stage IIIC-IV	
	-	**or** fine needle aspiration proving the presence of carcinoma cells in patients with a suspicious pelvic mass if CA125 (KU/L)/CEA (ng/mL) ratio is > 25. If the serum CA125/CEA ratio is ≤ 25, imaging or endoscopy is obligatory to exclude a primary gastric, colon or breast carcinoma
abdominal metastases:	involvement of the superior mesenteric artery	
	diffuse deep infiltration of the root of the small bowel	
	diffuse and confluent carcinomatosis of the stomach and/or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy	
	multiple parenchymatous liver metastases in both lobes	intrahepatic metastases
	tumor involving large parts of the pancreas (not only tail) and/or the duodenum	infiltration of the duodenum and/or pancreas and/or the large vessels of the ligamentum hepatoduodenale, truncus coeliacus or behind the porta hepatis
	tumor infiltrating the vessels of the lig. hepatoduodenale or truncus coeliacus	
extra-abdominal metastases:	not completely resectable metastases, as eg. - multiple parenchymal lung metastases (preferably histologically proven) - non resectable lymph node metastases - brain metastases	all excluding: - resectable inguinal lymph nodes - solitary resectable retrocrual or paracardial nodes - pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumors
patients characteristics / others	impaired performance status and co-morbidity not allowing a “maximal surgical effort” to achieve a complete resection	
	patients’ non-acceptance of potential supportive measures as blood transfusions or temporary stoma	
Criteria for interval debulking:	- upfront surgical effort in an institution without expert surgical skills / infrastructure - barrier for initial surgery has disappeared (eg. improved medical condition) - **not,** if reason for primary chemotherapy was tumor growth pattern diagnosed during open surgery by an experienced gynecologic oncologist under optimal circumstances (as in GOG study 152)	- No progressive disease, **and** - In case of extraabdominal disease at diagnosis the extraabdominal disease should be in complete response or resectable, **and** - Performance status and co-morbidity allowing a maximal surgical effort to no residual diseases.