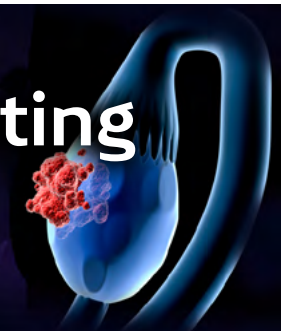
ANZGOG Annual Scientific Meeting 2024 Conference Review™



Making Education Easy

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In this review:

Abbreviations used in this review:

CIN2+ = cervical intraepithelial neoplasia grade 2+; **cfDNA** = circulating cell-free DNA; **ctDNA** = circulating tumour DNA; **dMMR** = mismatch repair deficiency; **HGSC** = high-grade serous ovarian cancer; **HPV** = human papillomavirus; **HR** = homologous recombination; **NSAID** = non-steroidal anti-inflammatory drug; **WGD** = whole genome duplication.

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Welcome to our review of the 2024 ANZGOG (Australia NZ Gynaecological Oncology Group) Annual Scientific Meeting held in Wellington, New Zealand.

With the theme "*Breaking down barriers in gynaecological cancer care*", this year's meeting provided a rich programme dedicated to improving access to and provision of optimal cancer care for all patients, while exploring the latest developments in the field. Here I discuss some of the highlights, beginning with two presentations which describe the patterns and barriers to ovarian cancer care worldwide and in the Pacific, highlighting the disparities of gynae-oncological care in our neighbouring low- and middle-income countries. The following two sessions discussed promising data on the accuracy and uptake of self-collection screening for cervical cancer, which may help to reduce mortality rates in traditionally hard-to-reach patients. Another fascinating study shows that recent aspirin use before a diagnosis of epithelial ovarian cancer is associated with increased cytotoxic T cell infiltrates, although no such associations were observed for NSAIDs.

I trust you find this conference review interesting and informative, and I welcome your feedback.

Kind Regards,

Associate Professor Philip Beale
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Exploring patterns of care and barriers to ovarian cancer care: results from a global expert-opinion survey study with an Australian/New Zealand regional perspective

Speaker: Rhonda Farrell (Central Clinical School, University of Sydney, Australia)

Summary: Worldwide, there are disparities in survival rates among patients with ovarian cancer. This presentation reported on a survey which investigated the patterns and barriers of ovarian cancer care across the globe, highlighting relevant data for Australia/NZ (ANZ) and neighbouring nations in Oceania/South-East Asia (OSEA). A total of 115 countries responded (n=1059), of which 102 were from ANZ/OSEA. Most respondents were gynaecological cancer surgeons (94%), while 24%, 25% and 51% of respondents were from high-, middle- and low-income countries, respectively. Compared to high- and middle-income countries, low-income countries had significantly lower rates of regional networks (p<0.001), cancer registries (p=0.001) and patient advocacy groups (p<0.001). Although a high proportion of middle- and low-income countries reported using international guidelines (100% and 96.2%, respectively), the goal of surgery in these countries was significantly less likely to be "*no macroscopic disease*" (p=0.021), with 26.9% and 21.2% aiming to achieve "*macroscopic disease present <1.0cm*". Middle- and low-income countries were also significantly less likely to perform resection of the bowel (p=0.003), resection of the upper abdomen (p<0.001), a total peritonectomy (p=0.008) or to strip the diaphragm (p<0.001). Across all income categories, the key barriers to optimal care were advanced presentation, co-morbidities, and social factors such as support systems and patient travel. Additional barriers reported by low-income countries included a lack of access to pathology/radiology and systemic agents, and treatment costs.

See comment on next page.

The international reality of cervical cancer: Pacific focus

Speaker: Michael Burling (Gynaecologist, St George Hospital, Sydney, Australia)

Summary: In this session, Dr Burling shared data on the state of cervical cancer in the Indo-Pacific region. He also outlined the structure of EPICC (Elimination Partnership in the Indo-Pacific for Cervical Cancer), a framework designed to support the global WHO strategy to accelerate the elimination of cervical cancer as a public health problem. Globally, cervical cancer is the fourth most common cancer among women, and in low-middle-income countries, it is the second most common. Of the 604,000 new cervical cancer cases and 342,000 associated deaths in 2020, 25% were from the Indo-Pacific region, and 90% were from low-middle-income countries. In NZ and Australia, the majority of women diagnosed with cervical cancer (≈80%) are never- or under-screened. Modelling has demonstrated that if WHO cervical cancer elimination targets were achieved in 78 low-middle-income countries, we could avert 300,000-400,000 deaths by 2030, 14.6 million deaths by 2070, and 62.6 million deaths over the course of the century. The EPICC approach aims to support WHO's elimination goals through six Priority Areas of Work: 1) Strengthening primary prevention via HPV vaccination support; 2) Secondary prevention via HPV screening and pre-cancer treatment; 3) Laboratory strengthening for screening and early treatment; 4) canSCREEN™ Digital Health Registry for strengthened models of care and decision-making; 5) Supporting cervical cancer management (treatment & palliative care); and 6) Policy/modelling across all elimination pathways.

Comment: These two presentations were a very sobering reminder of the disparities of gynae-oncological care in low- and middle-income countries. The survey conducted by Dr Farrell showed that the expectations in high-income countries were quite different to low- and middle-income countries, with standout issues including lack of access to drugs and services, and costs of treatment being major barriers. Dr Burling highlighted from first-hand experience of working in Fiji that the lack of radiation services means many women do not receive appropriate treatment for cervical cancer, and access to services in Australia/NZ is very limited and expensive. The fact that there is only one trained gynae-oncologist in Fiji, very limited medical oncology services, and no radiation machines, means that providing good care is very hard. This means that many women will die prematurely, and also will not have good symptom control. This can only be turned around by major investments of time, money and training. However, while the rates of cervical cancer screening are low by Australian and NZ standards, Dr Burling presented a success story of point-of-care test-and-treat in Tuvalu, where 76% of eligible women between the age of 30-49 years have received screening.

Urine high-risk human papillomavirus testing as an alternative cervical screening strategy

Speaker: Jennifer C Davies (Gynaecological Oncology Research Group, University of Manchester, UK)

Summary: In the UK, only 68.2% of women invited to partake in cervical screening actually attend, with many reporting embarrassment or discomfort with speculum examination, or restricted access to appointments. HPV urine testing may be a preferable alternative screening tool. The respective aims of the ACES Colposcopy and ACES Primary Care studies were to a) explore the efficacy of urine HPV testing for detecting cervical intraepithelial neoplasia grade 2+ (CIN2+); and b) determine the acceptability of urine-based cervical cancer screening. In the ACES Colposcopy study, 465 patients with abnormal cervical screening were randomised 1:1 to urine collection via the Colli-Pee collection device, or a standard pot. The sensitivity of urine for CIN2+ detection was 90.32% (95% CI 83.71—94.90), while the sensitivity of matched cervical samples was 97.58% (95% CI 94.81—99.11; relative sensitivity 92%). When inadequate urine samples were removed from the analysis, the sensitivity of urine sensitivity for CIN2+ detection improved to 91.80% (95% CI 85.44—96.00; relative sensitivity 93%). In the ACES Primary Care study, 1221 general screening attendees self-collected urine using the Colli-Pee collector, before undergoing routine screening. The specificity of urine sampling was found to be 85.76% (95% CI 83.66—87.69), while matched cervical samples had a specificity of 88.18% (95% CI 86.21—89.95; relative specificity 97%). Overall, urine-based screening was deemed to be acceptable; 62.4% of patients preferred urine sampling or had no preference.

Update on cervical screening

Speaker: David Hawkes (Director Molecular Microbiology, Australian Centre for the Prevention of Cervical Cancer)

Summary: David Hawkes discussed a report which used data from the National Cervical Screening Programme to measure the uptake of self-collection for cervical cancer screening in Australia. He shared that after the eligibility expansion in July 2022, there has been a consistent increase in the uptake self-collection, from 10% in Q3 of 2022 to 27% in Q4 of 2023. This increase was particularly high among the most disadvantaged quintiles (28%-29%), 70-74 year olds (34%), those who live in the Northern Territory (47%) and in very remote areas (51%). Among 30-74 year olds who had never been screened, the uptake of self-collection increased from 13% to 33%; among the under-screened, this increased from 14% to 40%. In 2022, 4% of screening tests occurred in women who had switched from clinician-to self-collected screening; this increased to 19% in 2023. The report concluded that self-collection is helping to improve access to screening and overcome barriers for traditionally hard-to-reach groups such as older women, and for those who are under-screened.

Comment: These two reports highlight some of the changes that have been occurring in the way samples are collected for cervical cancer screening. These also have implications for disadvantaged populations, including those in the Pacific. The presentation by David Hawkes was an update on data regarding self-collection for cervical cancer screening. The data showed that self-collection was being used increasingly by Australian women throughout 2023. More importantly, it demonstrated increases in the rates of screening in the never- and under-screened populations, which will hopefully lead to changes in mortality from this cancer. The other consideration is the capacity for this test to be done rapidly, cheaply and reliably. The presentation by Jennifer Davies discussed the role of urine sampling as an alternative method of screening. This seems to be an attractive alternative for many women. The use of a specifically designed collection pot (Colli-Pee) increases the accuracy of the testing, and it compared favourably with cervical sampling. The method was acceptable to most women, although some still preferred clinician-based testing. The cost of this test is the other factor as to whether it is the best way to screen large populations.

Timing of whole genome duplication is associated with tumour-specific MHC-II depletion in high-grade serous ovarian cancer

Speaker: Nikki L Burdett (Peter MacCallum Cancer Centre, Melbourne, Australia)

Summary: Around 50%-60% of all primary ovarian cancers show whole genome duplication (WGD); WGD also seems to develop later following diagnosis, with previous data finding WGD in nearly 80% of tumours from end-stage, homologous recombination-deficient, high-grade serous ovarian cancer (HGSC). These investigators hypothesised that WGD may be advantageous for HGSC tumour cells, by generating genomic diversity, leading to unique transcriptional processes. Comparisons were made between significantly altered genes and pathways in tumours with WGD to those without, using whole genome and RNA sequencing data from two prior datasets (n=79 and n=166). Tumours with WGD were found to have significantly lower expression of 13 MHC class II genes, and significantly lower expression of the transcriptional activator of these genes, CIITA. Pathway analysis of tumours with WGD also found downregulation of immune pathways, especially the interferon gamma response. Compared to tumours which developed WGD later, or not at all, those with early WGD acquisition had the lowest expression of MHC-II, substantially lower MHC-II gene-related signalling between cancer cell subsets, and significantly poorer progression-free and overall survival.

Comment: This study gives a deeper understanding of the biology of ovarian cancer cells as they evolve and change over time with treatment. WGD is currently not used in clinical settings to stratify patients into good or bad prognostic groups. However, this work shows that early presence of WGD at diagnosis is associated with a worse outcome than those patients who do not have WGD. Of note though, with time and under the pressure of chemotherapy, the rate of WGD goes up, indicating developing resistance. This ongoing work shows that WGD is associated with lower expression of MHC-II genes, leading to downregulation of immune pathways. These data could lead to treatment pathways for those with intact MHC-II pathways, and could lead to better survival in patients treated in the first line.

Spatial and temporal multi-site whole genome sequencing identifies inter-tumour heterogeneity in high grade serous ovarian cancer

Speaker: Nikki L Burdett (Peter MacCallum Cancer Centre, Melbourne, Australia)

Summary: The objective of this study was to assess the heterogeneity of genomic alterations in HGSC. Researchers applied whole genome sequencing to a subset of 21 patients (median 5 tumours per patient), to examine mutations, structural variants, copy number and mutational signatures. All cases showed a somatic pathogenic *TP53* mutation, while eight had homologous recombination (HR) deficiency due to somatic/germline mutations, and three had *CCNE1* amplification. There was inter-tumour heterogeneity in mutations, mutational signature abundance and copy number profiles; temporal/special heterogeneity was also seen in prognostic biomarkers, including *MYC*. A total of 15 cases (71%) had WGD, although five of these had subclonal duplication in only a subset of primary tumour sites. Among the eight cases who had recurrent tumour samples, the status of WGD was sometimes inconsistent across different timepoints; some cases underwent more than one duplication, and in one case, duplication was present in all primary samples, but not in any of the relapse samples.

Comment: This study is an example of the frightening heterogeneity of ovarian cancer samples from individual patients. This highlights that there can be multiple subclones identified from different locations in the peritoneum, and the more of these, the more difficult it is to effectively treat. Genes such as *MYC* were used to identify this heterogeneity, and may be a way of stratifying patients in those who need escalation of treatment. WGD is currently not used in the clinic to decide on treatment pathways, but again could be used to stratify patients into good and bad prognostic groups. Hopefully with biomarkers such as *CCNE*, there will be effective treatments available in the near future as part of targeted approaches.

Circulating tumour DNA for monitoring of response to neoadjuvant chemotherapy in patients with high-grade serous ovarian carcinoma

Speaker: Elin Gray (Centre for Precision Health, Edith Cowan University, Perth, Australia)

Summary: As part of the iPRIME study, these investigators carried out molecular profiling of ctDNA before and after neoadjuvant chemotherapy in 58 patients with HGSC. Initial data suggest that residual ctDNA is indicative of a lack of complete response to chemotherapy, and that it detects resistant variants in their early stages. After three cycles of neoadjuvant chemotherapy, there was no detectable ctDNA among those with a complete pathological response. ctDNA showed specific gene variant mutations weeks earlier than CA-125 levels. Somatic mutations were identified in 65% of patients, most of whom had alterations in *TP53*.

Comment: This presentation accompanied the first results from the iPrime study, which will be available soon. This study was a phase II study of durvalumab and tremelimumab in combination with neoadjuvant carboplatin and paclitaxel in newly-diagnosed women with advanced HGSC. This translational study provides extra information about the usefulness of ctDNA and likelihood of early relapse. This analysis of ctDNA in blood post-operatively predated the time of tumour marker relapse and clinical relapse. The only issue with this is, what we do with this information in real time? How can we adjust treatment in the light of this information to truly get a better outcome for these patients?

ANZGOG TIPS trial: A pilot study testing individual interventions to optimize perioperative care in ovarian cancer surgery

Speaker: Alison Brand (Department of Gynaecological Oncology, Westmead Hospital, Australia)

Summary: Programmes for enhanced recovery after surgery (ERAS) typically involve bundles of care, although there is limited evidence as to whether all individual components are needed. This was a multicentre pilot trial which explored the necessity of carbohydrate loading and pregabalin in patients with advanced ovarian, fallopian tube or peritoneal cancer. Eligible patients (n=47) from Australia and NZ were randomised 1:1:1 to either carbohydrate-loading/control drink/no drink (blinded), and 1:1 to pregabalin/no pregabalin (open-label). The study was found to be feasible, in that all patients agreed to randomisation and took the oral interventions. Post-operative symptoms were generally well-tolerated, and non-tolerated symptoms were balanced between treatment arms. There were no differences between the three beverage arms in terms of time to three consecutive meals or time to first bowel motion. The placebo and pregabalin groups had similar times to first rescue analgesia, although the placebo group used a higher dose of oral morphine equivalents in the first 48 hrs (145 vs. 118, respectively). In the first 24 hrs following surgery, blurred vision occurred more frequently in the pregabalin group than placebo (14 vs. 8 episodes). Researchers concluded that the trial was safe; grade 3/4 complications occurred in four patients, and one patient randomised to no drink/placebo experienced aspiration pneumonitis. No deaths occurred. It was noted that further studies such as this may be able to optimise perioperative care for patients with advanced ovarian cancer.

Comment: This study showed that a perioperative intervention in patients undergoing surgery for ovarian cancer was feasible, and patients were willing to be randomised to different interventions. This is a really important area of research, as randomised trials are hard to achieve. Funding for these trials is also a huge challenge. Even though the trial did not show any significant differences in the arms tested, it lays a really good platform to look at other interventions of interest. It would also be possible to roll this type of trial to other gynaecological cancers, and possibly across tumour types. The benefits of this research could well show improvements in the wellbeing of patients - reducing the length of stay in hospital and preventing short-to-medium side effects. We look forward to the next iteration of this study.

Recent aspirin use is associated with increased cytotoxic T cell infiltrates in epithelial ovarian cancer

Speaker: Nicola S Meagher (The Daffodil Centre, University of Sydney, Australia)

Summary: Studies have demonstrated an association between aspirin use following a diagnosis of epithelial ovarian cancer and reduced mortality. It is posited that this association is mediated by an advantageous immune microenvironment and increased immune surveillance. Patients with a favourable prognosis have demonstrated increased odds of having tumour infiltrating CD8+ T cells. This study included eligible patients diagnosed with epithelial ovarian cancer across three clinical trials (total n=854), who provided self-reported data on aspirin or NSAID use prior to diagnosis. Patients who had used aspirin recently, before diagnosis, showed an increased likelihood of recently-activated cytotoxic T cells within the tumour (OR 1.40; 95% CI 1.00—1.97). Compared with those who had never used aspirin, patients who used ≥15 tablets per week had a significantly increased chance of infiltrating total (OR 2.22; 95% CI 1.04—4.73), cytotoxic (OR 1.94; 95% CI 1.05—3.60) and recently-activated cytotoxic T cells (OR 2.27; 95% CI 1.10—4.69). In contrast, no significant T-cell associations were reported for users of NSAIDs.

Comment: There have been a number of studies that have looked at the effect of aspirin on ovarian cancer risk and on outcome after treatment for ovarian cancer. A recent meta-analysis showed that frequent use (>5 days per week) reduced the risk of ovarian cancer by 13%, and more in patients with two or more risk factors for ovarian cancer. A study in Australia and NZ (the OPAL study), estimated that taking aspirin pre-diagnosis or after diagnosis improved survival. This abstract gives us some additional insight into the possible mechanism of action. This showed that recent aspirin use was associated with an increased chance of having activated T cells in the tumour samples. This is thought to be one way that the immune system can modulate the behaviour of the cancer cells. Interestingly, this effect was seen with aspirin, but not with other NSAIDs. A trial was started with aspirin in patients with *BRCA* alterations who were planning to undergo a prophylactic oophorectomy, to look at changes in the ovarian and fallopian tube tissue. Unfortunately, this trial had to be stopped before completion. Further work in the space is welcomed, as it may be a simple way to improve outcomes for patients - especially those with specific subtypes.

MLH1 promoter methylation detection in endometrial cancer through ctDNA analysis

Speaker: Julia Matas (University of Melbourne, Australia)

Summary: This presentation from Julia Matas was awarded Best Poster at ANZGOG 2024. Loss of *MLH1* expression occurs as a consequence of *MLH1* promoter methylation, leading to mismatch repair deficiency (dMMR). Here, Julia discussed a non-invasive assay that has been developed to detect tumour-derived *MLH1* promoter methylation through ctDNA analysis, as an alternative to tumour tissue analysis. Julia demonstrated that her team's non-invasive ctDNA approach is feasible for rapidly identifying methylation *MLH1* promoter status in patients with advanced endometrial cancer. Her team developed a method which required only 5ng of plasma-extracted circulating cell-free DNA (cfDNA), and 1ng of the digested product was examined with droplet digital PCR to determine levels of *MLH1* methylation. In this research, ctDNA was successfully extracted from all participants in the phase II PHAEDRA trial who had evaluable plasma samples. Analyses of ctDNA are ongoing to assess *MLH1* methylation status, and data are awaited which will compare the results with matched tumour tissue assessments.

Comment: This assay is a step forward in a way to identify patients who have tumour-derived *MLH1* promotor methylation. This has been demonstrated to be accurate, and can be done in real time. In the samples from the PHAEDRA trial, there was correlation with all of the patients who had been demonstrated to have tissue methylation, and in one patient who had received chemotherapy, there was a change from no methylation to methylation. The results of the PHAEDRA trial showed that those patients with dMMR had a high response to single-agent immunotherapy (>50%), and therefore, having this test available for patients at different time points after treatment could easily direct clinicians to give the most appropriate treatment.

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Independent commentary by Associate Professor Philip Beale

Philip Beale is a medical oncologist who practices at the Concord Hospital in Sydney. He has had a long history of involvement in clinical research into gynaecological cancers, having been the chair of ANZGOG and now a board member, as well as part of the RAC. He has been the principal investigator in many studies and has over 140 peer-reviewed publications. He also has an interest in gastrointestinal cancers and is a member of AGITG.