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## Rethinking Ovarian Cancer: Recommendations for Improving Outcomes

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**Abstract**

There have been major advances in our understanding of the cellular and molecular biology of the human malignancies collectively referred to as ovarian cancer. At a recent Helene Harris Memorial Trust meeting, an international group of researchers considered actions that should be taken to improve the outcome for women with ovarian cancer. Nine major recommendations are outlined in this Perspective.

Patient prognosis has improved significantly for many solid cancer types. However, survival of women with epithelial ovarian cancer has changed little since platinum-based treatment was introduced over 30 years ago<sup>1-3</sup> (Figure 1). Invasive epithelial ovarian cancer is widely viewed and treated as a single disease entity with little stratification of histological or molecular subtypes. At a recent Helene Harris Memorial Trust (HHMT) meeting of leading ovarian cancer researchers and clinician-scientists, sponsored and organised by Ovarian Cancer Action (Box 1), we asked the question ‘*what actions can we take to improve the outcome for women with ovarian cancer?*’ A consensus regarding the major barriers to success and the most pressing questions led delegates to propose nine priorities for action, which we describe in this Perspective.

## Ovarian cancer is many diseases

The group felt it was essential that researchers, pathologists, epidemiologists and clinicians understood that ovarian cancer is a general term for a series of molecularly and etiologically distinct diseases that simply share an anatomical location. Recent pathological and genomic findings indicate that many ovarian cancers are derived from non-ovarian tissues and that the different histotypes share few molecular similarities (Figure 2)<sup>4</sup>. For example, the distal fallopian tube has been identified as a source of high-grade serous ovarian cancers<sup>5-7</sup>. The relative importance of the fallopian tube versus the ovarian surface epithelium in the genesis of high-grade serous ovarian cancers is still debated, however, the finding has important implications for screening, prevention and understanding the molecular biology of the disease. Clear cell and endometrioid cancers have a strong epidemiological link with endometriosis. High frequency somatic mutations of the PI3K catalytic subunit *PIK3CA* and AT-rich interactive domain-containing protein 1A (*ARID1A*) in adjacent endometriotic lesions link endometriosis, clear cell and endometrioid cancers<sup>8-10</sup>. The majority of invasive mucinous cancers are metastases to the ovary<sup>11,12,13</sup>. Improved histotype classification using immunological markers and genomic studies has shown that many tumors previously designated high-grade endometrioid cancers should be classified as serous cancers<sup>14-16</sup>. Low-grade invasive tumors are still regarded as ovarian-derived, but the initiating cells are unknown and it is possible that their site of origin will be re-evaluated in the future. Nevertheless, it is clear that serous borderline cancers are not precursor lesions for the majority of high-grade serous ovarian cancer, as they have a distinct spectrum of mutational events<sup>17</sup>.

Further sub-classification of histotypes is based on signaling pathway activation<sup>18</sup>, genomic events or gene expression profiling<sup>19</sup>. Some ovarian cancers have more in common with certain types of renal or breast cancer than other ovarian histologies. For example, high-grade serous ovarian cancers share genomic and transcriptional features with basal-like breast cancers<sup>17, 20</sup>. Ovarian clear cell cancers have similar expression phenotypes to renal and uterine clear cell cancers<sup>21</sup>, and women with ovarian clear cell cancer may benefit from the use of drugs such as sunitinib that are active in renal cancer patients<sup>22</sup>. Taking a rigorous view, the ovarian histotypes should be regarded as distinct diseases, as their cell of origin, epidemiology, and driver mutations are quite different.

The term ‘ovarian cancer’ is therefore misleading. It is not a single disease, and a significant proportion of tumours may not arise from ovarian tissue. The unifying clinical feature is frequent loco-regional dissemination to the ovary and related pelvic organs. We considered whether ‘ovarian cancer’ should be replaced with ‘pelvic’ or ‘peritoneal’ cancer but recognised the confusion that might ensue for patients, physicians and the literature, especially during a transition period. It is appropriate to allow the changed view to become more widely understood before the term is abandoned.

## Improved clinical trial design

The second action point was that there should be a shift in the emphasis from Phase III to nimble, earlier phase trials that explicitly include molecular studies. Given the differences in ovarian cancer subtypes, clinical trials should no longer aggregate the various histologies. Trial design should also consider molecular parallels with other solid cancers. Clinical reporting and scientific publications should use reproducible diagnostic methods and standardized terms for these disease entities<sup>23</sup>. The current single approach to treatment should rapidly evolve to evidence-based stratification based on molecular drivers and histotype-specific treatments.

The ovarian cancer field lags in incorporating targeted therapies into standard treatment (Figure 3). With the possible exception of poly(ADP-ribose) polymerase (PARP) and angiogenesis inhibitors (see below), single agent molecularly targeted therapies have only yielded small increments in progression-free survival in ovarian cancers. A major shift in the way clinical trials are designed is therefore urgently required. The ceiling in efficacy witnessed with all-inclusive Phase III trials means that the priority should now be subtype specific (randomised) Phase II clinical trials, based on sound scientific rationale. In addition, 'window trials'<sup>24</sup> with clear readouts of pathway inhibition that correlate with clinical outcome, will expedite clinical investigation of novel therapies.

Improved blood and imaging biomarkers that accurately measure response and residual disease are also needed; the current criteria are an impediment to better evaluation of response. Contrast-enhanced computed tomography (CT) imaging is the standard nonsurgical method for staging and assessing response, however, it is difficult to detect small peritoneal deposits. For example when peritoneal disease is <1cm, the sensitivity of CT is only 7–28%, and this is further dependent upon anatomical location<sup>25</sup>. Measurement of circulating levels of the ovarian tumour antigen CA125 (also known as Mucin-16) is routinely used to monitor disease recurrence, however, markers that are molecularly-based and sensitive for low volume residual disease are needed. Preliminary results from detection of cellular by-products of ovarian cancer cells in blood are promising but need wider evaluation<sup>26</sup>.

## Prevention and early detection

The third action point was to recognize that identification of patients at increased genetic risk currently offers the most effective measure for prevention and early detection of disease. High-grade serous ovarian cancer is diagnosed at an advanced stage in approximately 70% of patients, and these women have a significantly worse outcome than those with early stage disease. It is important to recognise that the poor prognosis in advanced stage disease is a function of at least two factors – the extent of disease and therefore the ability to remove the tumour surgically, and differences in the biology of tumours that remain confined to the pelvic space versus those that disseminate widely<sup>27</sup>. Early detection tests should focus on identifying the precursors of advanced stage high-grade serous ovarian tumours, rather than the molecularly distinct stage I/II low-grade tumours with Ras pathway activation, which are typically not precursors of more lethal tumours.

Traditional concepts of metastasis are difficult to apply to ovarian cancer. In high-grade serous carcinoma originating from the ovarian surface or fallopian tubes, or clear cell cancer arising in endometriotic deposits, there is no anatomical barrier to seeding throughout the peritoneal cavity. Emerging insights into disease progression of high-grade serous ovarian cancers now suggest that early detection of low-volume advanced stage, rather than early-stage, ovarian cancer may be a more realistic goal of screening studies<sup>28</sup> although the

clinical value of this strategy remains to be determined. More data about the natural history of precursor lesions in the fallopian tube epithelium and their rate of transformation to invasive carcinoma is needed to plan future screening methods and technologies<sup>29</sup>. Recent data from the Prostate, Lung, Colorectal and Ovarian (PLCO) trial indicate that current serological diagnostics and imaging tests are insufficiently sensitive to alter outcome in screened populations<sup>30</sup> although results from the large UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial remains to be reported. Based on current data, widespread screening is not yet justified and its value in the management of high-risk women is unknown<sup>31</sup>. Screening for endometrioid and clear cell ovarian cancer will be particularly challenging since endometriosis is a common, often subclinical, disease and risk factors for transformation have not yet been identified. Identification of women carrying germline mutations in *BRCA1*, *BRCA2*, *RAD51C* and other DNA repair proteins provides the most effective preventative strategy for high-grade serous ovarian cancers, as removal of the ovaries and fallopian tubes can reduce risk of disease in carriers by 80%<sup>32, 33</sup>. Given the newly appreciated importance of the fallopian tube in the genesis of high-grade serous ovarian cancer, it is recommended that complete removal of the fallopian tube should become standard of care in any woman undergoing hysterectomy and/or oophorectomy. Removal of the ovaries (oophorectomy) in pre-menopausal women induces early menopause. As a consequence, and with the changed view of the role of the fallopian tube in ovarian cancer, some have recommended that only the fallopian tubes be removed (salpingectomy) in women with germline *BRCA1* or *BRCA2* mutations, or a strong family history of breast and/or ovarian cancer<sup>34</sup>. However, until comprehensive comparative data are available, the group felt it is premature to recommend that only the fallopian tubes are removed.

While there is no evidence that current screening strategies reduce mortality in high risk women, it seems inevitable that effective early detection screening must be coupled with the identification of those women at increased genetic risk, to reduce the number of false positives<sup>30</sup>. Advances in high throughput sequencing and mutation scanning offer the potential to greatly reduce the cost of mutation testing, and therefore extend testing to more women, especially women with high-grade serous ovarian cancers. Recent genome wide association studies have identified a number of new ovarian cancer risk loci<sup>35, 36</sup>, enabled by large cancer cohorts assembled by research consortia (see below). Identification of novel genetic risk loci is improved by histotype stratification<sup>35, 36</sup>, and therefore genetic and epidemiological studies of tumours should embrace the appropriate classification of ovarian cancer.

## Identification of new targets

The fourth action was to recognize the need for novel approaches to identify therapeutic targets. Over the last decade, increasingly comprehensive genomic analyses of ovarian cancer have failed to reveal new oncogenic drivers in the more common histotypes. Large scale gene expression<sup>19</sup>, DNA copy number<sup>37, 38</sup> and mutational screens<sup>39</sup> have not identified new high frequency drugable targets in high grade serous ovarian cancers, perhaps with the possible exception of CyclinE1 gene (*CCNE1*). *CCNE1* amplification is associated with poor outcome<sup>40</sup> and oncogene addiction *in vitro*<sup>41</sup>. Further studies are needed to validate the prognostic significance of other amplified genes in high grade serous ovarian cancers and develop therapeutic approaches to targeting them. Mutations in the RAS pathway are found in more than 70% of low-grade serous ovarian cancers and specific clinical trials for this unique serous neoplasm are urgently needed. Activating mutations in *PIK3CA*<sup>8</sup>, and amplification of receptor tyrosine kinases including *MET*<sup>22</sup> and *ERBB2*<sup>42</sup>, provide novel therapeutic approaches in clear cell cancers. Although high frequency novel

somatic mutations have been found in granulosa<sup>43</sup> and clear cell<sup>10</sup> ovarian cancer, these uncommon subtypes only account for a small fraction of the disease mortality.

Genomic studies have reinforced the centrality of mutations in the tumour suppressor TP53<sup>20</sup>, *BRCA* pathway disruption<sup>44</sup> and homologous recombination repair (HRR) deficiency in high-grade serous ovarian cancers. The notion that many high-grade serous ovarian cancers are *BRCA*-like through alterations in other proteins in the HRR pathway<sup>45</sup> has resulted in exploration of PARP inhibitors<sup>46</sup>. Preliminary findings suggest efficacy of PARP inhibitors in a number of settings, including the use of olaparib as maintenance treatment after chemotherapy in women with platinum sensitive recurrent high-grade serous ovarian cancers<sup>47</sup>. About half of all high-grade serous ovarian cancers show disruption of the *BRCA* pathway either by germline or somatic mutation, or epigenetic silencing of pathway members<sup>39</sup>. Consistent with mutational studies<sup>39</sup>, functional assays show that roughly half of all high-grade serous ovarian cancers have defective formation of HRR foci following DNA damage<sup>48</sup>. If the repair-defective tumours correspond to those patients with relatively good responses to PARP inhibitors, this may provide an important predictive test of response. These data suggest that mutator phenotypes in high-grade serous ovarian cancer offer a valuable approach to novel therapies<sup>49, 50</sup>. Synthetic lethality as a strategy for targeting DNA repair and p53 pathways in high-grade serous ovarian cancer should be further explored with RNA interference and small molecule screens.

One of the most challenging aspects of high-grade serous ovarian cancer is the recognition that widespread gene expression and DNA copy number changes provide extensive opportunities for adaptation and the development of resistance<sup>17</sup>. Ongoing genomic instability may drive intra-tumoral genetic heterogeneity and increase the probability of treatment-resistant clone selection<sup>51, 52</sup>. Genetic alterations in tumour cells are not the only contributor to therapy resistance. Cell-non-autonomous effects are mediated by the tumour microenvironment, which is recruited by the tumour cells (see also below), providing a cytokine milieu on which the tumour thrives, becomes resistant to current therapies, and becomes more invasive. Single agent treatment is likely to be ineffective when cancerous cells are capable of utilising other non-targeted pathways. Therefore, it is crucial that we develop combination therapeutic approaches that anticipate tumour adaptive responses to individual targeted agents. The exploration of novel combinations of targeted therapeutics will only be possible if we can overcome the current reluctance of the pharmaceutical industry to be involved in clinical trials that combine drugs from different companies. Combination studies must be underpinned by preclinical investigation of dosing schedules in appropriate model systems.

## The tumor microenvironment

The fifth point was to emphasize the importance of targeting the tumour microenvironment as an adjunct to other molecular therapeutics and chemotherapy. The inherent instability of the genome of high-grade serous ovarian cancer has shifted attention to targeting the tumor microenvironment, which comprises a large proportion of the cell mass of many ovarian cancers. To date, encouraging results have been obtained with trials in ovarian cancer that target the angiogenic factor VEGF using the therapeutic antibody bevacizumab. The addition of bevacizumab to conventional chemotherapy improves progression-free survival in relapsed, platinum-resistant ovarian cancer<sup>53</sup>. In addition, large randomised phase III trials investigating the role of maintenance bevacizumab in the first-line setting (GOG218, ICON7) and in platinum-sensitive relapsed disease (OCEANS) have been completed. The results of all three trials, presented in abstract form only, suggest improvements in progression-free survival when given as concurrent or maintenance therapy. However, despite the presumed stability of the tumor endothelium, resistance to anti-VEGF agents has



emerged. Understanding resistance pathways and developing predictors of patient response are crucial to better exploiting anti-angiogenic therapies<sup>54, 55</sup>.

A spontaneous anti-tumour immune response in the form of tumour-reactive T cells and/or antibodies has been demonstrated in some patients with ovarian cancer<sup>56, 57</sup>. The increased infiltration of lymphocytes in tumour islets, predicts significantly longer survival in ovarian cancer<sup>58</sup>. *Vice versa*, the detection of high numbers of T regulatory cells, which mediate immune suppression, predicts poor patient survival<sup>59, 60</sup>. Additional immunosuppressive cell subtypes, such as B7-H4 expressing tumour macrophages,<sup>61</sup> have also been correlated with poor outcome.

Complex networks of inflammatory cytokines and chemokines<sup>62</sup> regulate communication between malignant cells and supporting stroma in ovarian cancer. These cytokines and their intracellular signalling pathways can make malignant cells resistant to apoptosis, facilitate evasion of tumour immunity and promote angiogenesis. Tumour cells typically trigger inflammatory cytokine networks as a means to escape immune recognition in spite of surrounding inflammation<sup>63, 64</sup>. In experimental animal models, targeting these key inflammatory cytokines and chemokines has been shown to abrogate these processes that are key to the progression of ovarian cancer<sup>62, 65</sup>.

The association of intra-tumoral T cells with increased survival, and T regulatory cells with worse survival, indicates that ovarian cancers could respond to immune therapy. Pilot studies indicate that therapies capitalizing on pre-existing antitumour immune responses can be successful in ovarian cancer. For example, objective responses and/or prolonged survival have been seen with immune checkpoint blockade using an antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)<sup>66, 67</sup> and Phase II studies are currently underway. The understanding that select conventional chemotherapy drugs also have immunomodulatory activity offers new opportunities to design combinatorial approaches for women with ovarian cancer whose tumours exhibit pre-existing antitumor immunity in terms of high levels of intraepithelial tumour-infiltrating lymphocytes. In addition, trials targeting inflammatory cytokines<sup>68, 69</sup> are currently in early stages, but they can offer important biological lessons for clinicians.

There needs to be a rapid development of further Phase II/III studies focusing on agents targeting key pathways in the tumour microenvironment that not only assess their efficacy alongside established cytotoxic regimens, but also aim to establish the optimal use of these agents for maintenance therapy.

## Tumor adaptation and resistance

The sixth action point was that understanding clonal diversity, tumor adaptation and acquisition of resistance is essential if more durable responses to therapy are to be achieved. Many women respond well to first line treatment, but frequently relapse with chemotherapy-resistant disease. Evolutionary models of clonal selection may explain drug resistance in cancer. In acute lymphocytic leukaemia and chronic myeloid leukaemia, point mutations conferring resistance to imatinib exist at low prevalence prior to treatment and can become highly enriched during relapse<sup>70, 71</sup>. Autopsy studies on advanced pancreatic cancer have shown profound genetic heterogeneity, with 52% of mutations being present in sub-clonal populations<sup>72, 73</sup>. Whether this paradigm can explain resistance in ovarian cancer, and in particular whether heterogeneity is associated with primary platinum resistance, needs further investigation. With advances in nextgeneration sequencing we now have the tools to investigate clonal diversity and to start inferring the evolutionary changes that may contribute to resistance.

Despite the plethora of research dedicated to the mechanisms of platinum resistance, these are yet to translate to clinical practise. Undoubtedly, deficiencies in our knowledge of the fundamental changes occurring within the tumor – both the epithelial fraction and the microenvironment - throughout treatment have impeded progress. More recently, studies with paired tumour samples collected prior to treatment and following disease relapse have provided some of the first insights into clonal variation and mechanisms of resistance *in vivo*<sup>52, 74</sup>. Serially obtained biopsies of disease sites should be a central component in clinical trial design.

## Importance of international consortia

The seventh action point was that international consortia involving large biological datasets must be encouraged, but they require high fidelity and transparency in analytical approaches. Ovarian cancer is a relatively uncommon disease and, together with its histologic diversity, this makes it difficult to collect substantial numbers of samples of specific subtypes. With the increased recognition of the importance of stratification by subtype, global collaborations and consortia such as Ovarian Cancer Association Consortium (OCAC), The Cancer Genome Atlas (TCGA), The Australian Ovarian Cancer Study (AOCS), OCTIPS (Ovarian Cancer Therapy – Innovative Models Prolong Survival) and Ovarian Tumor Tissue Analysis Consortium (OTTA) are crucial to furthering our understanding of the molecular biology of ovarian tumors and genetic risk. Such collaborative endeavours require highly ordered, standardised and quality-controlled strategies for the collection and management of biological specimens. The combination of high-throughput technologies with large sample sets allows detailed biological and translational studies. However, the challenges of managing large molecular datasets, each identifying a multitude of putative abnormalities — many of which may prove to be artefacts — are significant. Moreover, the opportunity to introduce human operator error remains unacceptably high. Methodologies used in the analysis of such data sets should be wholly transparent, reproducible, and biologically validated in the laboratory before any such findings can be put into practice. Errors made in the development of the OvaCheck early detection test underscore the importance of rigorous biostatistical support, especially when dealing with complex molecular datasets<sup>75</sup>.

## Better experimental models

The eighth action is to speed the development of more appropriate experimental models, which should occur as a result of improved understanding of ovarian cancer. New model systems are needed that reflect the various originating cells, as well as the underlying genomic events driving each disease. Although mouse models of ovarian cancer have been developed<sup>76–79</sup>, these have not for the most part recapitulated human disease. A model that recapitulates the oncogenic drivers and biology of high-grade serous ovarian cancer has remained elusive. Mouse transgenic and knockout studies are likely to benefit substantially from improved understanding of the key driver mutations, such as loss of *ARID1A* in clear cell cancer and the importance of secretory cells of the fallopian tube in high-grade serous ovarian cancer. Recent reports of fallopian tube-based model systems will help define the physiology and susceptibility of this epithelium to transformation<sup>7, 80</sup>.

Now that it is appreciated that clear cell, mucinous, low-grade endometrioid and high-grade serous ovarian cancers are as molecularly distinct as, for example, breast and renal cancer, researchers must pay strict attention to the human cell line models they use to explore different aspects of the disease. Comparative molecular studies that fail to recognise the histopathological origins of the ovarian cancer cell lines used are no longer appropriate. Currently, the origin of many of the ovarian cancer cell lines are poorly defined - the field



would benefit enormously from the creation of new lines that reflect the different histotypes and molecular subtypes.

It is also timely to consider *in vitro* models that are more appropriate than 2-dimensional growth of cells on plastic. Three-dimensional culture systems that mimic the peritoneal microenvironment have provided important insights into ovarian cancer biology<sup>8182</sup>.

## Quality of life and symptom benefit

The ninth action was that quality of life and symptom benefit should be included with response and survival rates as a primary endpoint in clinical trials investigating palliative treatment. The primary endpoint of most clinical trials has traditionally been objective response and survival. Most patients relapse after first line treatment; response rates and time to progression typically diminish with each recurrence. Although there are numerous studies of palliative chemotherapy regimes in platinum resistant ovarian cancer, there is scant evidence to confirm that these treatments are truly palliative and improve symptom control<sup>83</sup>. Attempts to address this important question with the currently available quality of life questionnaires have not been successful, and toxicity data completed by physicians may give a false impression of the patient's experience. Robust instruments are needed that measure the impact of palliative chemotherapy on symptom control given that this should be the major aim of treatment. Treatment should be stratified in accordance to prognosis, with more emphasis being placed on minimizing side effects and avoiding inappropriate therapy in patients with a low likelihood of benefit. Prognostic indices are required to better categorize patients with recurrent ovarian cancer into poor, intermediate and good subsets rather than the current approach of grouping patients together.

## Conclusion

The last five years have seen an explosion in our understanding of the heterogeneity of ovarian cancer. This comes with an emphatic commitment to changing in the way that clinical trials in ovarian cancer must be designed. Treatment in ovarian cancer will benefit from the careful alignment of target, drug, patient, and trial design. The greatest challenge will be to craft combinations of therapy that result in years of improved survival. There is an outstanding level of cooperation and willingness to share ideas amongst those in the ovarian cancer research field, as exemplified by the HHMT meeting. A high level of cooperation bodes well for the women whose lives we hope to improve.

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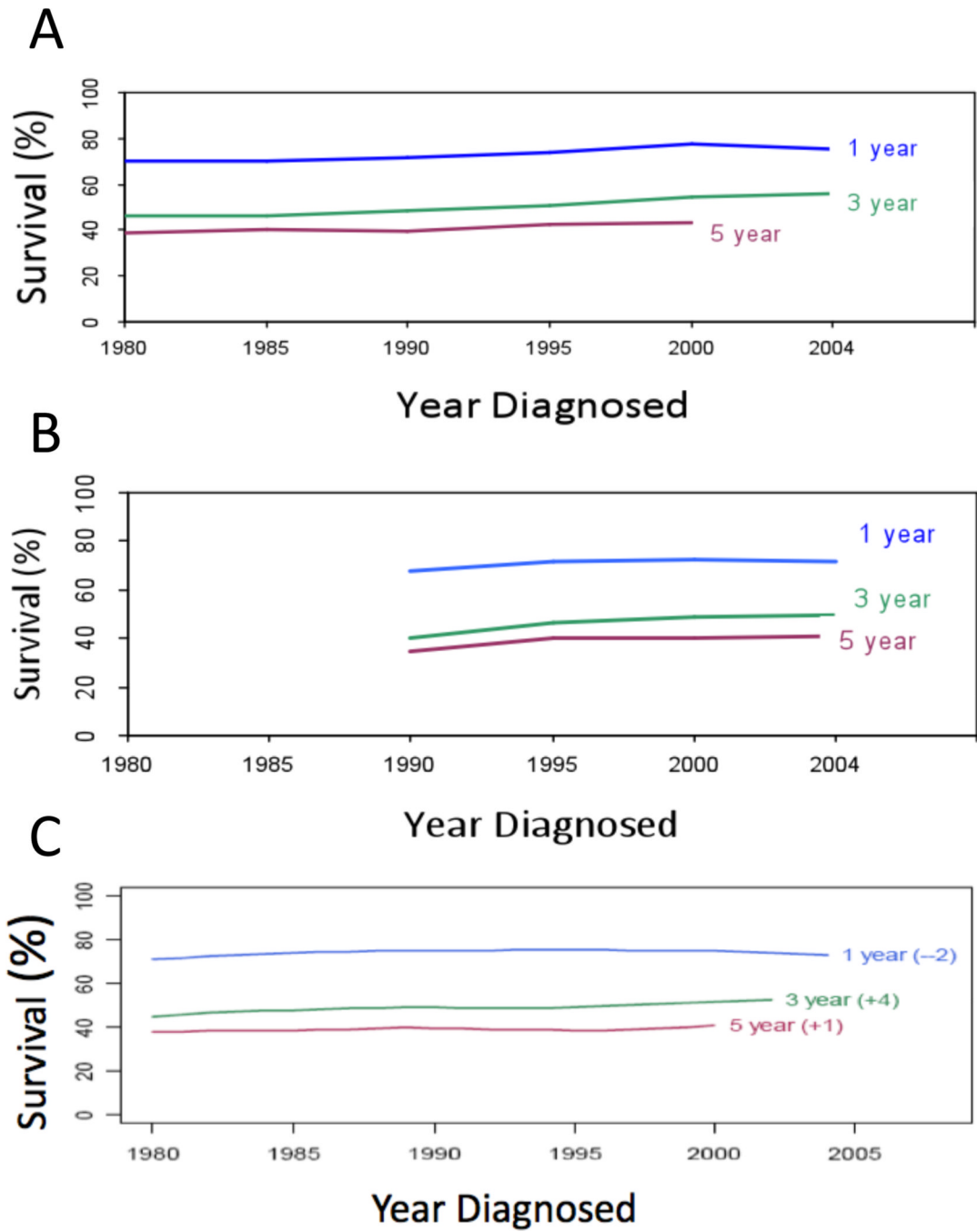
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**Box 1: The meeting**

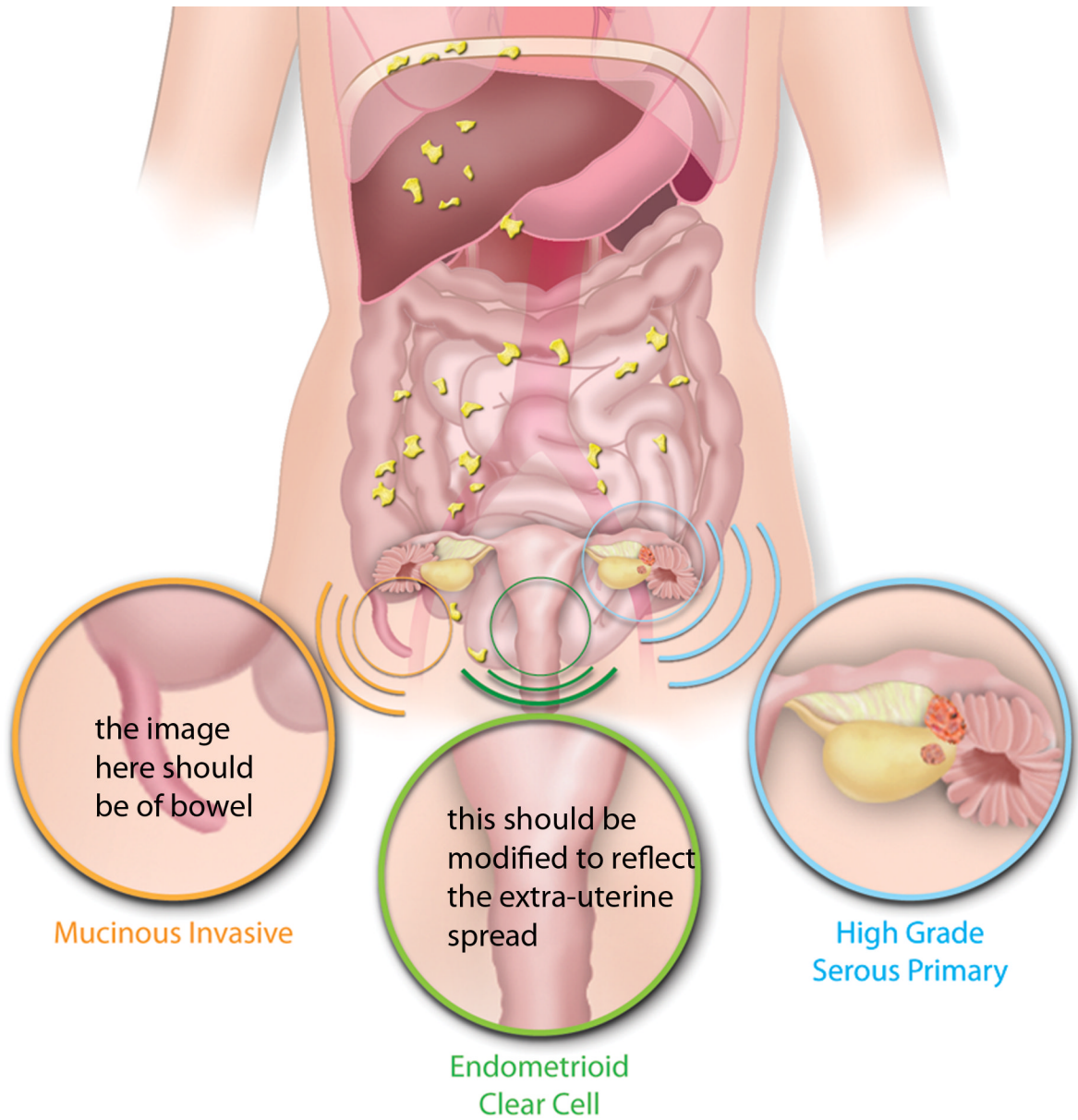
For twenty-five years the Helene Harris Memorial Trust has recognised the importance of communication between scientists and clinicians in improving the early detection of ovarian cancers and treatment of patients with advanced disease, bringing together international experts on a biannual basis <http://www.ovarian.org.uk/>. In January 2011 researchers met in Florida over 4 days to consider the latest findings in basic, translational and clinical research in ovarian cancer. With a both a sense of optimism associated with recent advances and frustration with limited improvements in outcomes in the past, we considered new ways forward based on recent findings. The delegates attending the meetings are outlined in Supplementary Table 1. The resulting review reflects the consensus of the meeting and the listed authors have all contributed to the manuscript.

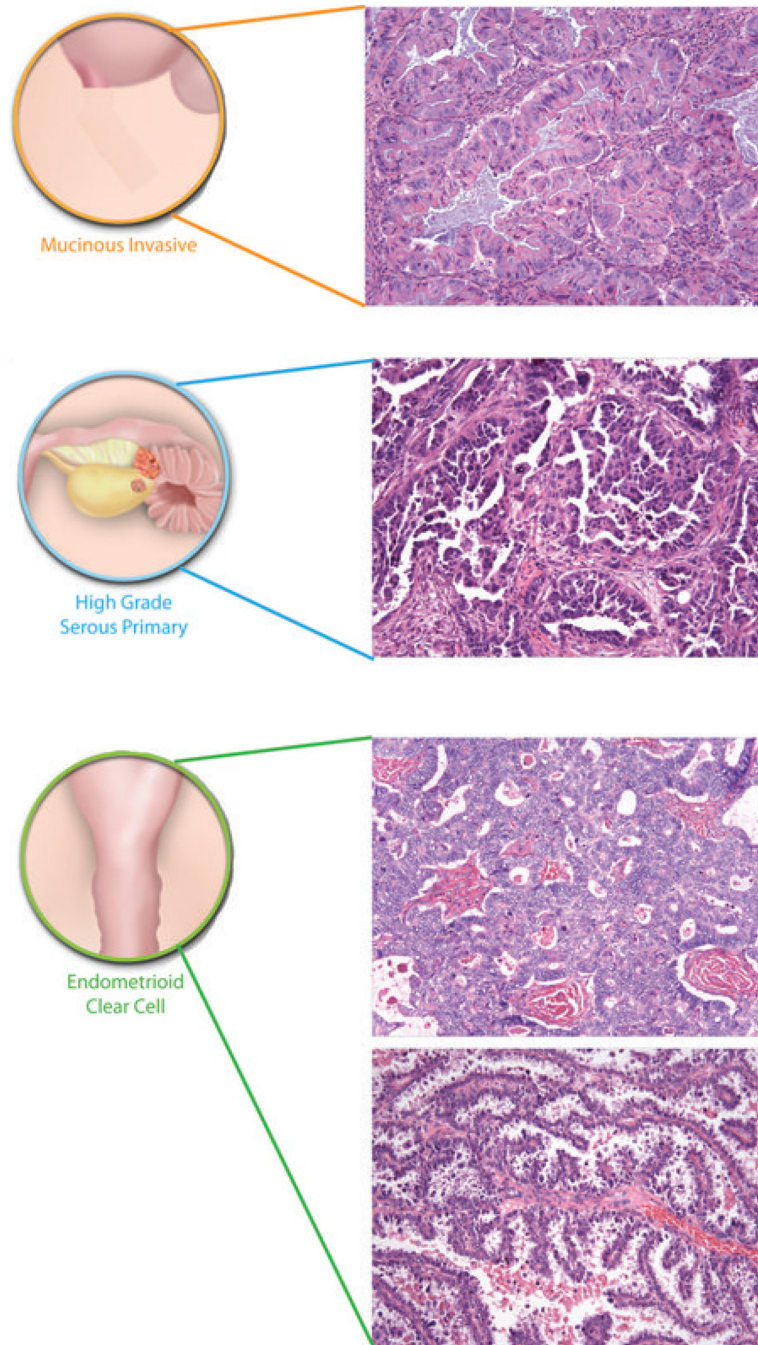




**Figure 1. Survival from ovarian cancer**

One-, three- and five-year survival post-diagnosis of ovarian cancer patients over the past 20 years. Data from: A) Surveillance, Epidemiology and End Results (SEER, 1980–2004); B) The Cancer Council of Victoria, Victoria, Australia (1990–2004); C) The Cheryl Brown Outcomes Unit, British Columbia, Canada (1980–2004).

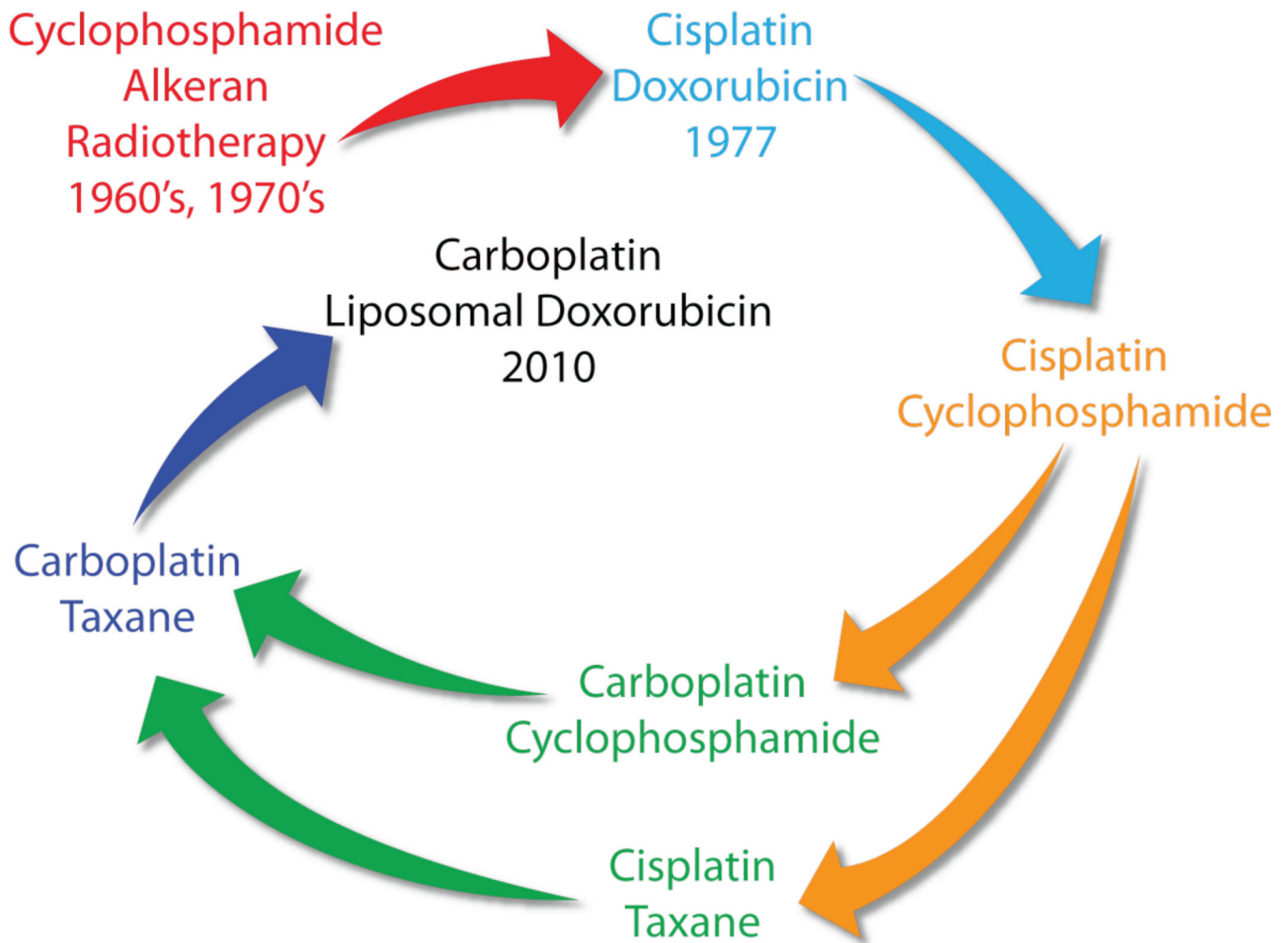




**Figure 2. The origins of ‘ovarian’ cancer**

Ovarian cancer is a collective term for invasive cancers derived from different tissues. A majority of invasive mucinous ovarian cancers are metastases to the ovary, often from the gastrointestinal tract including colon (Co), appendix (Ap) or stomach (St). Endometrioid and clear cell ovarian cancers are derived from endometriosis, which in turn is associated with retrograde menstruation (blue arrow) from the endometrium (En). High grade serous ovarian cancers are derived from the surface of the ovary (Ov) and/or distal fallopian tube (FT) - the relative contribution that the two sites make to these tumours remains unclear. Benign and low malignant potential (borderline) tumours are not included in the diagram. Such tumours are thought to be of ovarian origin, however, the originating cells are not defined and their

derivation may be revised in the future. Histological images courtesy of R. Drapkin, Dana-Farber Cancer Institute, USA, and C. Crum, Brigham and Women's Hospital, USA.



**Figure 3. Evolution of chemotherapy for ovarian cancer over the last 50 years**

It has proved difficult to progress beyond platinum-based therapy, which was introduced in the late 1970s and remains standard of care. Cisplatin and subsequently carboplatin, which has a lower toxicity profile, have been combined with other agents, including taxanes. Most recently, liposomal doxorubicin has become commonly used with carboplatin, especially in a relapse setting. It is notable that the combination of carboplatin and liposomal doxorubicin involve similar drugs to those used in the mid-70s, albeit with reduced side-effects. It is likely that ovarian cancer treatment will evolve significantly in the coming years with the introduction of molecularly targeted agents, such as the poly(ADP-ribose) polymerase PARP inhibitors, histotype-specific treatments, and dose dense regimes, including use of weekly taxane.