

1 Cell Carcinoma of the Ovary: A report from the first Ovarian Clear Cell  
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31 **Abstract**

32 Recent literature has highlighted histological subtypes of ovarian carcinoma as distinct diseases,  
33 each with unique clinical and molecular features. Of the major histological subtypes of ovarian  
34 epithelial cancers clear cell carcinoma of the ovary is the second most common subtype  
35 representing 5-25% of all ovarian carcinomas depending on the population being studied.

36 Historically, this diagnosis has been of concern to both patients and physicians due to reports that  
37 clear cell carcinoma is associated with a worse prognosis than the more common serous subtype  
38 of ovarian carcinoma. In June of 2010, a group of researchers and clinicians convened in  
39 Vancouver, to review and discuss the clinical, pathologic, molecular, and treatment-related  
40 features of clear cell carcinoma of the ovary. This review summarizes the information presented  
41 and discussed at this conference.

42

## 42 **Introduction**

43 The histological subtypes of ovarian carcinoma are distinct diseases, each with distinct clinical  
44 and molecular features [1-3]. Clear cell carcinoma (CCC) of the ovary is the second most  
45 common subtype of ovarian carcinoma (OC) representing 5-25% of all OC depending on the  
46 population being studied. Historically, this diagnosis has been of concern to both patients and  
47 physicians due to reports that CCC is associated with a worse prognosis than the more common  
48 serous subtype of OC [4]. In June of 2010, a group of researchers and clinicians convened in  
49 Vancouver, to review and discuss the clinical, pathologic, molecular and treatment-related  
50 features of CCC. This review summarizes the information presented and discussed at this  
51 conference.

52 *Ovarian cancer and subtype-specific abbreviations used in this manuscript:* clear cell carcinoma  
53 (CCC), high-grade serous carcinoma (HGSC), serous carcinoma (SC), ovarian carcinoma (OC),  
54 endometrioid carcinoma (EC), epithelial ovarian cancer (EOC).

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## 56 **Epidemiology of Clear Cell Cancer**

57 There are significant geographic differences in the prevalence of CCC. Studies in North America  
58 and Europe quote prevalences of 1-12%[5-8] whereas the prevalence in Japan is as high as 15-  
59 25% [9, 10]. Data from Japanese gynaecologic committee shows that the prevalence of CCC  
60 increased between 2002 and 2007 from 19% to 24.7%[11, 12]. In women living in the United  
61 States, CCC was diagnosed twice as frequently in Asians (11.1% vs. 4.8% in whites)[13].

62 In SEER data reported by Chan *et al.*, women with clear cell histology were younger than  
63 patients with serous cancers (55 vs. 64 years; median age)[13]. The diagnosis of CCC is also  
64 more commonly associated with thromboembolic complications [4, 14, 15]. Up to 40% of  
65 patients with CCC may develop thromboembolic disease and this rate is double that in matched  
66 non-CCC controls with ovarian cancer [14]. In one case-control study CCC was associated (odds  
67 ratio of 2.3) with an increased body mass index (BMI) [16]. Race was not assessed in this study  
68 and it should be noted that results from other published studies on BMI and CCC are inconsistent  
69 [16-19].

70 Ovarian CCC usually presents as a pelvic mass. Recent reports involving large institutional  
71 cohorts compared low-stage to high-stage ovarian cancers (I/II vs. III/IV) and showed that 57-  
72 81% of CCC were diagnosed at stage I/II [9, 20]. In a retrospective review involving four centres  
73 in Japan on more than 600 patients over 10 years, 49% of CCC were stage I compared to 17% of  
74 SC [9], and in SEER data, 56% of CCC were stage I compared to 19% for SC [13]. These  
75 remarkable differences in stage distribution may account for much of the variation in reported  
76 frequencies of CCC between different trials. Combining the low overall incidence of CCC and  
77 their early-stage propensity, CCC may make up only 1-5% of high-stage patients in  
78 chemotherapy trials [5].

79 It has long been recognized that CCC is associated with endometriosis [21, 22]. In keeping with  
80 the higher incidence of CCC in Asian women, some studies have reported higher prevalence  
81 rates of endometriosis in Asian women [23]. Endometriosis associated ovarian cancers tend to  
82 occur in younger women and present on average 5-6 years earlier than high-grade serous  
83 carcinoma (HGSC) [24]. It has been suggested that atypical endometriosis might be a malignant  
84 precursor of ovarian cancer [25, 26]. Subsequently, a large Japanese population-based study

85 confirmed that endometriosis results in a nine-fold increase in the risk of ovarian cancer[27].  
86 With the recent discovery of mutations in *ARID1A* noted in almost half of CCC[28, 29], there is  
87 renewed interest in research to define the molecular events that define the precursor lesions of  
88 CCC. Understanding the molecular basis for this disease may help explain many of the unique  
89 prognostic features of CCC subtype.

## 90 **Molecular and Genomic Biology of Clear Cell Cancer**

91 When compared to the more common, HGSCs of the ovary, CCC are understudied and as a  
92 consequence less well understood, Table 1 summarizes significant molecular features that have  
93 been highlighted in current literature. In contrast with HGSC, CCC are almost invariably *TP53*  
94 wild-type [2, 30-34] and have a lower frequency of *BRCAl/2* germline mutations [35]. In  
95 keeping with this CCC are generally characterized by a low level of chromosomal instability and  
96 relatively low proliferation rates [2, 10]. CCCs have the highest frequency (up to 40%) of  
97 *PIK3CA* mutations among OC[33, 36], and it has been suggested that the PI3K-AKT-mTOR-  
98 HIF (phosphoinositide 3-kinase, v-akt murine thymoma viral oncogene homolog, mechanistic  
99 target of rapamycin, and hypoxia induced factor) pathway may be a therapeutically viable target  
100 [37, 38].

101 Both traditional karyotypic and array-based CGH measures of DNA copy number have identified  
102 common regions of gain including, amongst others, 17q23-25[39-41]. This correlated with  
103 increased expression of the 17q23 protein-phosphatase gene *PPMID* [39]: a negative regulator  
104 of p38/MAPK, and in turn, p53-mediated transcription and apoptosis, as well as a negative  
105 regulator of CHK1 and G2/M cell cycle arrest[42]. Over-expression of *PPMID* appears linked to  
106 poor outcome[40] while a CCC cell line with amplification at 17q23 is selectively sensitive to

107 PPM1D inhibition[39]. The protein-phosphatase 2A (PP2A) complex has also been shown to be  
108 involved in G2/M checkpoint control[43, 44] and the scaffolding subunit of Protein Phosphatase  
109 2 (PP2A), *PPP2R1A*, was found to be mutated in ~5% of ovarian clear cell carcinomas [28].  
110 Mutations appear to be clustered around conserved repeated HEAT motifs [28][and Huntsman  
111 unpublished data] that mediate binding of a regulatory subunit within the complex, and a pro-  
112 oncogenic modification of function has been suggested [28].

113 Similarities in the gene expression profiles of clear cell tumours from renal, endometrial, and  
114 ovarian sites have raised the possibilities of potential crossovers of molecular marker expression,  
115 and therefore possible common therapeutic strategies focussed on specific targets [45]. IGF2BP3  
116 has been reported and validated as an independent prognostic marker for both renal clear cell  
117 carcinomas and ovarian CCC[46, 47]. The VHL target, HIF1a, also appears to be expressed at a  
118 higher level in ovarian clear cell carcinoma compared to other histological subtypes [[48],  
119 Michael Birrer and David Bowtell personal communications] and a recently described CCC  
120 expression profile signature appears to centre around oxidative stress, hypoxia, and cytokine  
121 related pathways[49]. This pathway appears to involve IL-6 and STAT3 converging on  
122 HNF1B[50], the hypoxia induced transcription factors HIF1A and EPAS1[[49], Michael Birrer  
123 and David Bowtell personal communications]. This latter crossover from renal clear cell  
124 carcinomas is further legitimized in a handful of anecdotal reports and case studies using multi-  
125 targeted kinase inhibitors such as Sunitinib [51]; David Bowtell personal communication].

126 Although classically described targets of Sunitinib (PDGFRB, KIT, VEGFR)[52] do not appear  
127 to be highly overexpressed in CCC, Sunitinib appears to potently target a broad spectrum of  
128 tyrosine kinases and growth factor receptors[53]. Although there are suggestions that sunitinib  
129 acts predominantly on the microvasculature [54], a recent study describing a clear cell specific

130 gene signature based on cell lines would support many of sunitinib's wider spectrum of targets  
131 being expressed dominantly in the tumour epithelium[49]. Although, there are many similarities  
132 between ovarian and renal CCC it is important to note that they are not the same disease. In  
133 particular, both somatic and germline abnormalities of the *VHL* gene are associated with renal  
134 carcinomas but have not been reported in ovarian CCC (0/74 ovarian samples in COSMIC<sup>1</sup>).  
135 However, positive immunoreactivity seen in both hereditary and sporadic renal carcinomas can  
136 also be observed at a relatively consistent and high level in ovarian CCC[55].

137 Most recently, the tumour suppressor *ARID1A* has been shown to be mutated in almost half of  
138 CCC cases[28, 29]. The *ARID1A* gene product (BAF250A) is a component of the SWI/SNF  
139 chromatin-remodelling complex [56-58] and this complex interacts with a number of hypoxia  
140 and cytokine related transcription factors, including HIF1[59] and STAT3[60]. In leukaemia cell  
141 lines *ARID1A* was shown to be essential for the response to FAS-induced apoptosis [61]. While  
142 the precise spectrum of molecular events and their interactions are still being mapped out for  
143 CCC an overall picture is emerging linking cytokine and hypoxia signalling and transcriptional  
144 control via the SWI/SNF complex.

## 145 **Pathology of Clear Cell Cancer**

146 CCCs, being relatively uncommon, have posed diagnostic challenges for pathologists in the past.  
147 In a recent review of 575 low-stage OC, 23% of clear cell carcinomas identified at review were  
148 not reported as such at the time of original diagnosis [62] CCCs are composed of glycogen  
149 containing clear, hobnail, or oxyphilic cells and often display an admixed tubulocystic or  
150 papillary architectural pattern (it is rarely solid; Figure 1). The characteristic glycogen-rich  
151 nature of CCC is echoed in the molecular features where an enrichment of glycogen metabolism

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<sup>1</sup> Catalogue of Somatic Mutations in Cancer, <http://www.sanger.ac.uk/genetics/CGP/cosmic/>

152 genes is seen compared to HGSC[49]. CCCs are composed of glycogen containing clear,  
153 hobnail, or oxyphilic cells and often display an admixed tubulocystic or papillary architectural  
154 pattern (it is rarely solid; Figure 1). The characteristic glycogen-rich nature of CCC is echoed in  
155 the molecular features where an enrichment of glycogen metabolism genes is seen compared to  
156 HGSC [[49] and Bowtell unpublished data]. The stroma occasionally contains abundant  
157 basement material. The grade of the nuclear atypia varies and there is usually low mitotic  
158 activity. Frozen section diagnosis can be challenging with only 41% of cases correctly classified  
159 in this study [49]Immunohistochemical marker panels may be helpful in cases of uncertainty,  
160 particularly when distinguishing between CCC and HGSC histology. An immunohistochemical  
161 marker panel including HNF1B, WT1 and ER and can be used (CCC are HNF1B positive and  
162 WT1 and ER negative, while HGSC show an opposite staining pattern)[63].

163 Historically, so-called mixed carcinomas with clear cell and high-grade serous components were  
164 particularly problematic with respect to diagnostic reproducibility. On the basis of clinical, and  
165 immunohistochemical features, and histopathological features such as mitotic index, these mixed  
166 tumours are indistinguishable from HGSC and therefore the term HGSC with clear cell features  
167 was suggested [64], indicating that they are a variant of high-grade serous carcinoma and  
168 unrelated to CCC.. Though rare, mixed clear cell/endometrioid carcinomas account for 1.3% of  
169 all ovarian carcinomas and are the most common mixed ovarian carcinoma [8]. The finding of  
170 mixed endometrioid/CCC may not be surprising since both subtypes of OC are associated with  
171 endometriosis and have reported mutations *ARID1A* and the PI3K pathway.

172

## 173 **Treatment Considerations**

174 Refined use of morphological criteria has dramatically increased the inter-observer  
175 reproducibility in the diagnosis of ovarian carcinoma cell type (kappa 0.90), including CCC [65]  
176 and immunohistochemical marker panels can be used in difficult cases [66]. Contemporary  
177 pathology review can provide excellent diagnostic accuracy in CCC. It should be noted that the  
178 most common ovarian cancer subtype, HGSC, is used as the comparison group throughout this  
179 article, however many studies have not distinguished between high-grade and low-  
180 grade/borderline serous tumours. Evidence now suggests these are in fact different entities and  
181 not part of continuum of serous tumours [2, 3, 66-68] and therefore combining them in clinical  
182 research can be expected to confound analysis. Whenever possible we will make the distinction  
183 between studies where HGSC versus serous carcinomas (SC) that are not further specified were  
184 studied.

### 185 ***Surgery***

186 There are several considerations relating to the surgical management of ovarian clear cell  
187 cancers. Because between 49%-56% of CCC present as stage I disease it is important to  
188 understand determinants of prognosis and the effectiveness of postoperative treatment in this  
189 group with apparently limited disease.. In a retrospective Japanese study, staging was not  
190 associated with improved survival in 205 CCC cases [69]. Further subgroup analysis was not  
191 performed in order to delineate a low-risk group and most patients (>80% in each group)  
192 received chemotherapy. Takano *et al.* retrospectively studied 199 early-stage (clinical pT1)

193 patients from multiple institutions in Japan. Lymphadenectomy was preformed in 135(68%)  
194 patients and was positive in 10 cases [70]. When progression-free survival was examined  
195 according to lymph node status (positive vs. negative vs. unknown), both lymph node status and  
196 positive cytology/ascites were predictive of progression-free survival (PFS) on univariate  
197 analysis, with only positive cytology maintaining significance on multivariate analysis for PFS.  
198 The hazard ratio for positive node status was 3.7 (confidence interval: 0.4-32) versus 2.1  
199 (confidence interval: 1.0-4.2) for positive cytology/ascites although the . p-value for positive  
200 nodes was of borderline significance ( $p = 0.05$ ) for PFS. On multivariate analysis there were no  
201 factors in the clinical pT1 patients that were predictive of overall survival.

202 In Takano's study,[70] despite the fact that over 90% of patients received postoperative  
203 chemotherapy, there were a number of relapsed patients (3 of the 5 patients) in the node positive  
204 group that were long-term survivors. The details of these patients were not reported so that  
205 drawing definite conclusions about outcomes of the node positive patients in this study remains  
206 a problem as they influence the outcome of the multivariate analysis. As in this study, previous  
207 Japanese reports have implicated positive peritoneal cytology as an adverse prognostic factor  
208 with reports of significant relapse rates of approximately 35% in stage IC disease [9, 71]. This  
209 finding was also noted in a small series of 29 patients reported by Kennedy *et al.* in 1989 [21],  
210 and in an institutional study from British Columbia [20].

211 Historically, concerns relating to the prognosis of patients with the CCC subtype, even with low  
212 stage CCC most institutions recommended postoperative treatment. One adverse prognostic  
213 factor possibly influencing this decision is the high frequency of ovarian capsule rupture of CCC  
214 as reported in EORTC-ACTION trial[72]. Capsule rupture was reported in 44% of CCC versus  
215 19% in serous tumours. The vast majority (85%-90%) of cases were due to intra-operative

216 rupture at the time of surgery. Patients with CCC in this trial rarely had either obvious pelvic  
217 disease extension (3% vs. 10%) or bilateral tumours (2% vs. 10%) compared to serous cancers.

218 Recent data suggest that stage I CCC have a prognosis similar to stage I SC though outcome may  
219 be confounded by treatment and the accuracy of pathological diagnosis. In the SEER database,  
220 stage I CCC had a similar survival to SC (85.3% vs. 86.4%) [13]. This finding was also  
221 replicated in a large report on stage I patients with 5-year survivals of 76% and 73% for stage I  
222 CCC and SC respectively [73]. However, a study of ovarian cancer outcomes in British  
223 Columbia with contemporary pathology review found that the 10-year disease specific survival  
224 was 87% for 35 patients with stage Ia/Ib CCC compared to 68% for those with HGSC [20]  
225 (Figure 2). In this study, any sharp dissection of the adnexal mass from the pelvic sidewall  
226 resulted in tumours being considered stage II; the outcome for patients with stage II tumours was  
227 worse [75]. The most informative data regarding the comparative prognosis of CCC versus SC  
228 was published as a subgroup analysis of the EORTC-ACTION trial [72, 74]. CCC patients in the  
229 observation arm of this trial had a similar 5-year disease free survival (DFS) compared to SC  
230 (71% in CCC vs. 61% in SC;  $p=0.2$ , log-rank test). Further, CCC patients did not seem to benefit  
231 from chemotherapy as the DFS in the chemotherapy treated group (37 patients) was only 60%,  
232 and did not differ statistically from the 71% 5-year DFS (26 patients) in the observational arm of  
233 the study. Fertility-sparing surgery usually followed by postoperative chemotherapy has been  
234 reported in small numbers of patients and is an option in carefully selected patients [75, 76]. This  
235 data speaks to the need to identify patients with stage I disease who have a good prognosis where  
236 adjuvant therapy may not be beneficial, or identify those who do not seem to benefit from  
237 postoperative chemotherapy so this treatment can be avoided.

238 Based on current knowledge consideration should be given to surgical treatment only in  
239 surgically-staged patients with stage Ia CCC.

240 For patients with locally advanced or metastatic disease, surgery plays an important role.

241 Retroperitoneal node metastases may occur in 50-60% of patients with advanced disease [71].

242 Though patients with endometriosis may have more adhesions and scarring, these patients appear  
243 to have a better outcome than those without endometriosis, and surgical cytoreduction is feasible  
244 [77]. Surgical cytoreduction must be evaluated considering the fact that CCC is less responsive  
245 to chemotherapy [5, 78], and patients who have little or no response to first-line therapy are  
246 resistant to second-line therapy [79, 80].

247

## 248 ***Radiotherapy***

249 For almost 20 years radiation therapy has been known to confer a long-term survival benefit to  
250 patients with OC; the use of whole abdominopelvic radiation (WAR) in intermediate-risk  
251 patients (high risk stage I, stage II, and stage III – no residuum, or minimal residual disease  
252 limited to the pelvis) has also been shown to result in improved survival compared to pelvic  
253 radiotherapy due to a further reduction in the incidence of upper abdominal relapse[81].

254 Moreover, there is evidence that radiotherapy may improve survival when used as a  
255 consolidation therapy after chemotherapy[82, 83], and up to 70% of patients treated in a  
256 palliative setting with chemoresistant EOC experience complete resolution of symptoms [84].  
257 Radiation therefore is clinically effective in the management of patients with EOC.

258 Recent studies support a role for the use of WAR in early-stage (Ic/II) CCC. In 2007, Nagia *et al.*  
259 reported a small study in 16 patients with CCC (14/16 patients with stage Ic/II) whose outcomes  
260 were compared to historical controls treated with platinum-based chemotherapy. The 5-year  
261 overall survival of the radiation treated group was 83% compared to 33% for the platinum-based  
262 chemotherapy treated patients [85]. A much larger study with contemporaneous controls was  
263 reported by Swenerton *et al* [86]. This series of 700 patients contained 375 women with  
264 endometrioid, clear cell, and mucinous histologies. Patients were treated with platinum-based  
265 chemotherapy alone, or a combination of platinum-based chemotherapy with WAR. Although  
266 this was a retrospective study, the findings are intriguing. They found a significant improvement  
267 in survival for those patients with endometrioid, clear cell, and mucinous tumours who received  
268 combined therapy. There was a 40% reduction in cancer-specific deaths that translated into an  
269 improvement of 10-year survival rates by 26% (78% combined treatment vs. 52%  
270 chemotherapy). This subgroup of 375 patients included approximately 175 patients with CCC.  
271 Based on this information it would be prudent to consider undertaking a randomized trial in  
272 order to determine whether combined chemotherapy with WAR is more effective than  
273 chemotherapy alone or if early stage CCC tends to be confined to pelvis whether pelvic  
274 irradiation alone is better than chemotherapy.

## 275 ***Chemotherapy***

276 Traditionally women with CCC have been eligible for inclusion in front line and other  
277 chemotherapy trials involving epithelial ovarian cancer. These studies have resulted in the  
278 combination of carboplatin and paclitaxel being the standard of care, regardless of histological  
279 subtype, for the front line treatment of OC [87, 88]. The impact of platinum based chemotherapy  
280 or the prognosis of clear cell histology is difficult to assess due to the confounding effects of low

281 numbers of patients within any one clinical trial and stage of disease. As stated previously in this  
282 review CCC are disproportionately represented in early stage disease[7, 87, 89-94]. As a result,  
283 the Gynecologic Cancer Intergroup (GCIIG) consensus conference in 2004 could not reach a  
284 conclusion on the clinical significance of CCC histology. A Rare Ovarian Histologies Working  
285 Group was established which received international intergroup cooperation to create a database  
286 from completed randomised clinical trials to address prognostic questions surrounding CCC and  
287 other rare OC histological subtypes [95]. A meta-analysis of source data from over 8000 patients  
288 derived from seven international phase III platinum based first line studies was published in 2010  
289 [5]. Two hundred and twenty-one (2.5%) women with stage III/IV CCC were included in the  
290 analysis. In comparison to the reference histology, SC, women with CCC appeared to have  
291 worse outcomes with increased risk of death (HR=2.18; 95%CI 1.84–2.57) and disease  
292 progression (HR=1.64; 95%CI 1.41–1.92). Estimated median overall survival (OS) was 21.3  
293 months (95%CI 17.8-28.1 months) compared to a median OS of 40.8 months (95%CI: 39.7 to  
294 42.2) for SC. There was no statistical difference between studies with and without centralized  
295 pathology review. The authors conclude that the data support recent international collaborative  
296 efforts to enrol patients in histology specific studies [96].

297 Some investigators suggest that CCC may be relatively resistant to standard carboplatin  
298 paclitaxel chemotherapy. In retrospective series, response rates (RR to first line treatment are  
299 between 22 and 56%. This compares to RR over 70% in patients with SC [9, 71, 97-100]. Others  
300 report similar RRs for women with CCC compared to serous carcinoma, however as noted  
301 above, some analysis may be confounded by historical classifications of SC [79]. Response to  
302 further lines of chemotherapy on progression or recurrence of disease are, however, uniformly  
303 low. In a retrospective study of 39 patients, women who had no response or only a partial

304 response to first line treatment failed to respond to second line chemotherapy[79]. In a further  
305 study from Japan, 75 patients diagnosed with CCC treated with at least 2 cycles of second line  
306 chemotherapy were evaluated for response. Women relapsing greater than 6 months after initial  
307 treatment had a RR of 8% compared to a RR of 6% in those progressing within 6 months.  
308 Median OS was 16 months in the platinum sensitive and 7 months in the platinum resistant group  
309 [80]. New approaches to treating this disease are therefore urgently required.

310 Clear cell specific studies require multi-group collaboration and considerable effort by individual  
311 institutions to open studies, which may only recruit 1-2 patients/centre/year. However, despite  
312 these challenges there have been a number of studies for women with CCC. Based on data  
313 suggesting activity for the combination of irinotecan hydrochloride plus cisplatin (CPT-P) in  
314 women with CCC [101, 102], the Japanese Gynecologic Oncology Group (JGOG) conducted a  
315 randomized phase II study comparing CPT-P with carboplatin paclitaxel [103]. Both  
316 chemotherapy regimens were well tolerated with over 70% of women completing 6 cycles of  
317 treatment. There was no significant difference in progression-free survival (PFS) between the 2  
318 treatment groups. Nevertheless, in a subset analysis of women with less than 2 cm of residual  
319 disease, PFS tended to be longer in the CPT-P arm, although this did not reach statistical  
320 significance ( $p = 0.2702$ ). A multi-national phase III study lead by the JGOG is currently  
321 underway and the accrual target of 652 patients will be reached by the end of 2010.

322 The future for the treatment of clear cell ovarian cancer lies in translating the discoveries made in  
323 the laboratory into intelligently designed clinical trials utilizing targeted agents. These studies  
324 must be designed in such away as to maximize the opportunity to learn about this disease  
325 therefore high quality correlative studies are essential.

326 Targeting receptor tyrosine kinases is an attractive approach in CCC. Sunitinib malate is an oral,  
327 small molecule that inhibits tumour proliferation and angiogenesis targeting VEGFR, PDGFR,  
328 KIT, and a host of other tyrosine kinases and growth factor receptors[52, 53]. Sunitinib is highly  
329 active in the treatment of clear cell carcinoma in the kidney and is now approved as a standard  
330 treatment in this disease and in gastrointestinal stromal tumours[104, 105]. Anecdotally Sunitinib  
331 shows activity in CCC of the ovary[51]; Bowtell personal communication]. Since September  
332 2009 the GOG have been recruiting patients into a phase II study of women with persistent or  
333 recurrent CCC (NCT 00979992, Clinicaltrials.gov). Results from this study are eagerly awaited.  
334 Another attractive target based on the preclinical data is the PI3K-AKT-mTOR pathway, which  
335 plays an important role in apoptosis, metabolism, cell proliferation, angiogenesis, and cell  
336 growth[106]. Several mTOR inhibitors have entered phase I/II trials that include rapamycin and  
337 its analogues: Temsirolimus (CCI-779, Torisel; Wyeth Pharmaceuticals), Everolimus (RAD-001;  
338 Novartis), and Deferolimus (AP23573; ARIAD and Merck).[107] Initial data look promising in  
339 CCC, with 3 out of 6 (50%) patients responding to temsirolimus in a small series presented at the  
340 2010 American Society of Clinical Oncology Annual Meeting [108].

341 Exciting new therapeutic targets are emerging as we learn more about the biology of CCC. In  
342 translating these into successes for patients in the clinic, we still face the issues common to  
343 studying many rare tumour types. The current system of ethical and scientific review makes  
344 multi-institutional phase II studies of rare tumours difficult. This prevents women with rare  
345 tumours from participating in clinical trials and halts the needed progress to find effective new  
346 therapies for women with these tumours. Several approaches have been proposed to help us  
347 address this issue: International collaboration, potentially through the Gynaecological Cancer  
348 Intergroup (GCIG), is essential. The JGOG clear cell phase III study (which is approaching

349 completion) demonstrates that collaboration can be successful in this disease. Powered subsets  
350 within larger EOC trials may help address questions related to response in CCC. These solutions,  
351 however, do not address the “discovery phase” so vital to advancing development of targeted  
352 agents in any given tumour type. New approaches to clinical trial design are needed.

353 One such strategy would be to investigate a number of different rare tumours, possibly sharing  
354 common molecular features, in a single trial. This so called “Umbrella Trial” design would  
355 improve efficiency and potentially enable centres to open studies that would for one rare tumour  
356 type might not have been viable. To further maximize trial opportunities for these patients  
357 studies might incorporate a cross over design. For example, patients might start on  
358 Temsirolimus then switch to Sunitinib on progression. Essential components of these studies  
359 would be expert pathological review and tissue collections to enable high quality correlative  
360 studies that would complete the “translational loop” back into the laboratory. Novel approaches  
361 are vital to this disease to inform future research and select the best agent(s) for investigation in  
362 larger scale international clinical trials.

## 363 **CONCLUSIONS**

364 The first step in developing tools to improve cancer control for this disease is to recognize that  
365 CCC represents a distinct clinical problem. CCC of the ovary has little in common with HGSC  
366 of the ovary other than sharing a site of presentation (Table 2). It stands to reason that little gain  
367 will be made in binning CCC with high-grade serous carcinomas in laboratory or clinical studies  
368 unless the study is stratified and powered appropriately to perform an a priori defined subtype  
369 specific analysis. Considering the state of our current knowledge, important future strategies  
370 should include identifying the clinical, pathologic, and molecular determinants of those patients

371 with stage I CCC that are cured with surgery alone. In fact, there is evidence to suggest that those  
372 patients with surgically-staged Ia CCC may not benefit from adjuvant therapy. Patients desiring  
373 fertility sparing treatments would also derive benefit from the identification of such low-risk  
374 groups. For the time being, accurate surgical staging to exclude extra-ovarian metastases should  
375 be considered in protocols addressing surgery only. Patients with stage IC/II and more advanced  
376 disease seem to have a relatively poor prognosis[20] and therefore efforts should focus on  
377 finding effective therapies for this group. Radiation trials should be considered for these at-risk  
378 patients, either alone or in combination with chemotherapy. Finally, for patients with advanced  
379 disease novel approaches to clinical trial design will be of importance and Intergroup  
380 collaboration will be required in order to obtain adequate patient numbers. Studies using novel  
381 agents – for example PI3K-mTOR inhibitors, anti-angiogenics, and tyrosine kinase inhibitors –  
382 directed against disease-specific molecular targets identified in the laboratory are urgently  
383 needed.

384 **Figure Legends:**

385 **Figure 1:** Histology of (A) clear cell carcinoma (CCC) and (B) high-grade serous  
386 carcinoma (HGSC). CCC sample illustrates glycogen-rich clear tumour cells arranged in  
387 papillary architecture. The papillary core stroma contains homogeneous red basement  
388 membrane material. Note the absence of mitotic figure in the CCC in contrast to the  
389 HGSC in (B). The HGSC shows papillary architecture with slit-like spaces and severe  
390 nuclear atypia.

391

392

393 **Figure 2:** Kaplan Meier survival curves for low stage (I/II) ovarian carcinomas OS (A)  
394 and PFS (B) comparing clear cell carcinoma (CCC) to high-grade serous carcinoma  
395 (HGSC) suggests that survival of low stage CCC is favourable in comparison to HGSC.  
396 In contrast, OS (C) and PFS (D) for patients with high stage (III/IV) ovarian carcinomas:  
397 CCC histology appears to have worse outcome than serous (SC; grade not specified).  
398 Source data for A&B from a population based study [20], and for C&D from 7  
399 randomised clinical trials [5].

400

400 Table 1: Molecular Events in Clear Cell Ovarian Cancer

<b>GENE</b>	<b>DESCRIPTION</b>	<b>PATHWAYS EFFECTED</b>	<b>REF</b>
<i>ARID1A</i>	Loss of function & truncating mutations in ~50%	SWI/SNF chromatin remodelling (transcriptional changes)	[28, 29]
<i>HNF1B</i>	Clear cell lineage specific biomarker	Multiple – enrichment of transcription factor target genes in CCC expression profile	[49], Bowtell unpublished
<i>MTOR</i>	Higher levels of activated phospho-mTOR (IHC)	PI3K-AKT-mTOR-HIF	[37]
<i>PIK3CA</i>	Activating mutations seen in up to 40%	PI3K-AKT-mTOR-HIF	[28, 36]
<i>PPM1D</i>	Amplification and overexpression in ~10% of CCC	Negative regulation of p38/MAPK and G2/M (CHK1/CHK2)	[39, 40]
<i>PPP2R1A</i>	Clustered mutations in ~7% of CCC.	PP2A complex, G2/M checkpoint	[28], Huntsman unpublished
<i>PTEN</i>	Loss of protein expression ~1/3 of cases (IHC)	PI3K-AKT-mTOR-HIF	[109]
<i>TP53</i>	IHC rarely shows overexpression for p53 – presumed wild-type	Sensor of DNA damage & apoptosis	[2, 32, 34]

401

402

402 **Table 2:** Discriminating features of clear cell (CCC) and high-grade serous carcinoma (HGSC)

Clear Cell Carcinoma	High-grade serous carcinoma
<p>Presents at younger age and low stage (pelvic mass)</p> <ul style="list-style-type: none"> <li>• ~ 70% Stage I/II at presentation</li> </ul>	<p>Present at older age and high stage (ascites common)</p> <ul style="list-style-type: none"> <li>• ~ 80% Stage III/IV at presentation</li> </ul>
Associated with Endometriosis (putative precursor lesion)	Associated with serous tubal intraepithelial carcinoma (STIC; putative precursor lesion)
Low stage outcome better than (stage matched) HGSC	High stage outcome better than (stage matched) CCC
Higher proportion in Japanese/Asian populations (up to 25% of OC)	Higher proportion in European populations
Higher frequency of thromboembolic complications	Low frequency thromboembolic complications
Inherently chemoresistant to current treatment standards (Platinum/taxane)	Good initial response rates to current treatment standards (Platinum/taxane)
Low frequency of BRCA1/2 mutations	<p>BRCA dysfunction</p> <ul style="list-style-type: none"> <li>• Higher proportion of hereditary (germline) BRCA1/2 mutation carriers</li> </ul>
<i>TP53</i> wild-type	<i>TP53</i> mutant
Genomically stable	Genomically Unstable
High frequency of PIK3CA mutations (activating)	Low frequency of PIK3CA mutations
High frequency ARID1A mutations (loss of function)	No detectable mutation of ARID1A

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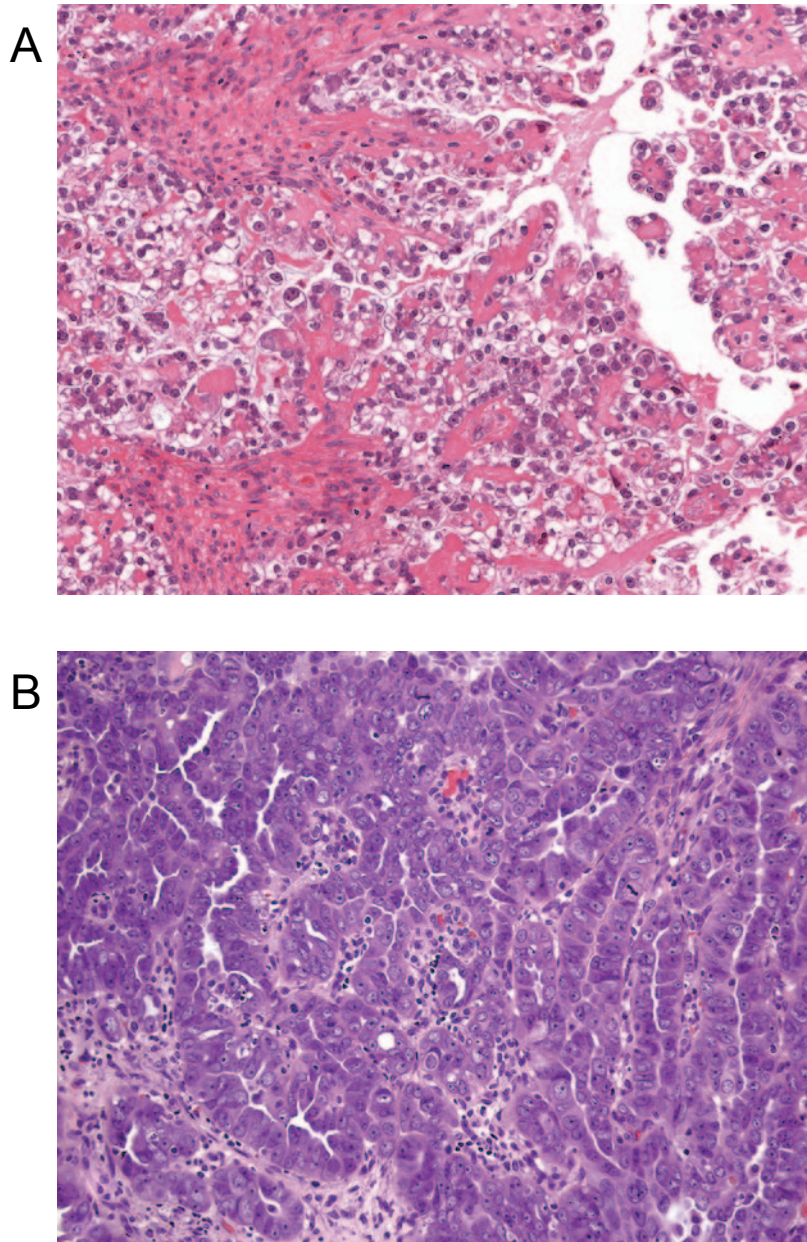
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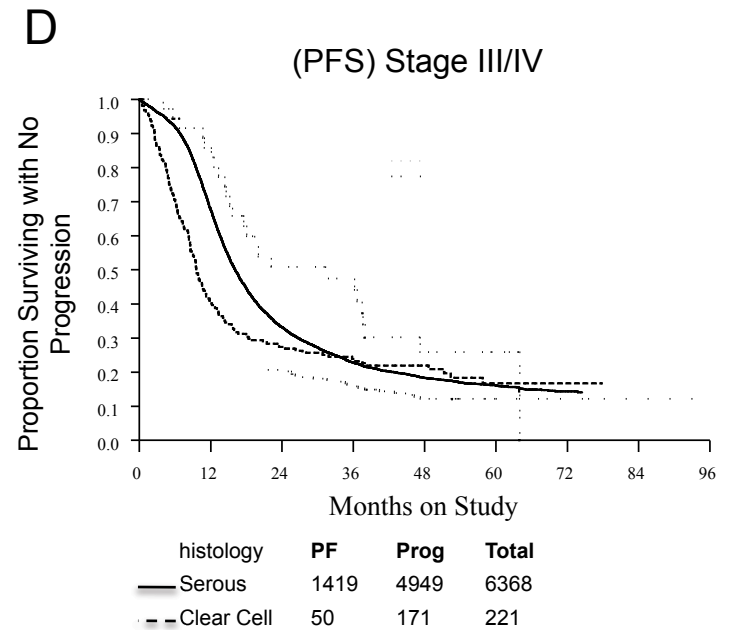
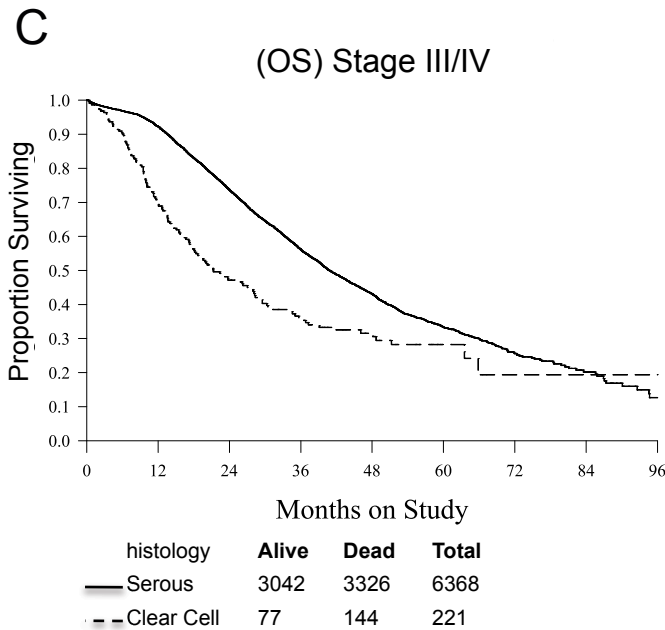
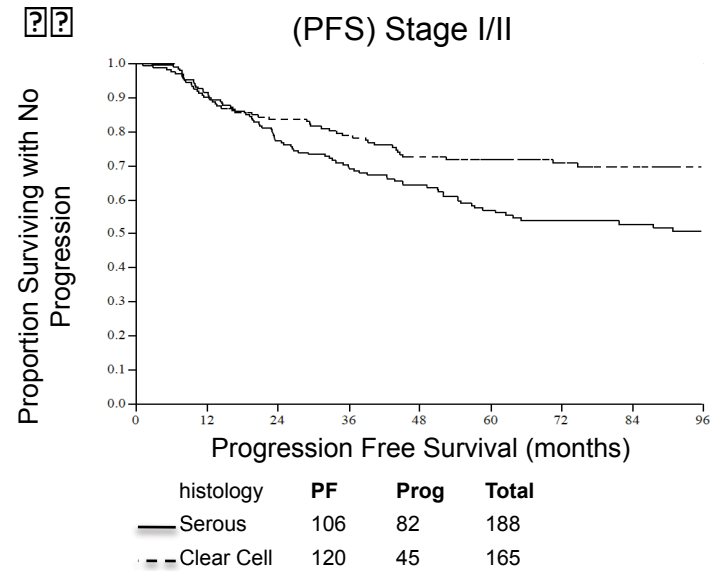
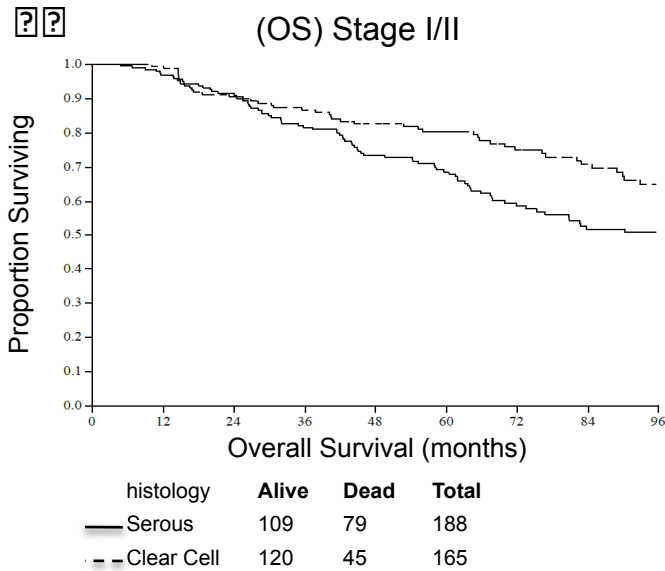
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**Figure 1:** Histology of (A) clear cell carcinoma (CCC) and (B) high-grade serous carcinoma (HGSC). CCC sample illustrates glycogen-rich clear tumor cells arranged in papillary architecture. The papillary core stroma contains homogeneous red basement membrane material. Note the absence of mitotic figure in the CCC in contrast to the HGSC in (B). The HGSC shows papillary architecture with slit-like spaces and severe nuclear atypia.



**Figure 2:** Kaplan Meier survival curves for low stage (I/II) ovarian carcinomas OS (A) and PFS (B) comparing clear cell carcinoma (CCC) to high-grade serous carcinoma (HGSC) suggests that survival of low stage CCC is favourable in comparison to HGSC. In contrast, OS (C) and PFS (D) for patients with high stage (III/IV) ovarian carcinomas: CCC histology appears to have worse outcome than serous (SC; grade not specified). Source data for A&B from a population based study [19], and for C&D from 7 randomised clinical trials [5].