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Patterns of clinicopathological features and outcome in epithelial ovarian cancer 1 patients: 35 years of prospectively collected data.

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1 **Title:** Patterns of clinicopathological features and outcome in epithelial ovarian cancer
2 patients: 35 years of prospectively collected data.

3
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16
17 **Shortened Title:** Patterns in ovarian cancer outcome over time.

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20

21 **ABSTRACT**

22

23 **Objective:** Investigate the clinical landscape of ovarian carcinoma(OC) over time.

24 **Design:** Register-based prospectively collected data.

25 **Setting:** South-East Scotland

26 **Sample:** 2805 OC patients diagnosed 1981-2015.

27 **Methods:** Survival times were visualised using the Kaplan-Meier method; median survival, 5-
28 year survival probabilities and associated restricted mean survival time analyses were used to
29 quantify survival differences

30 **Main Outcome Measures:** Disease-specific survival.

31 **Results:** Significant increase in disease-specific survival(DSS) from 1981-1985 to 2011-2015
32 was observed (median 1.73 vs 4.23 years, $p<0.0001$). Corresponding increase in progression-
33 free survival(PFS) was not statistically significant (median 1.22 vs 1.58 years, $p=0.2568$). An
34 increase in the proportion of cases with low residual disease volume (RD) ($<2\text{cm RD}$) following
35 debulking was observed (54.0% vs 87.7%, $p<0.0001$). The proportion of high grade serous
36 (HGS) cases increased ($p<0.0001$), while endometrioid and mucinous cases decreased
37 ($p=0.0005$ and $p=0.0002$). Increases in stage IV HGSOc incidence ($p=0.0009$) and stage IV
38 HGSOc DSS ($p=0.0122$) were observed. Increasing median age at diagnosis correlated with
39 increasing Eastern Cooperative Oncology Group Performance Status (ECOG PS) over time
40 ($r=0.86$).

41 **Conclusions:** OC DSS has improved over the last 35 years; PFS has not significantly increased,
42 highlighting that improvement in outcome has been limited to extending post-relapse
43 survival. Distribution of stage at diagnosis, histological subtype and RD following debulking
44 have changed over time, reflecting evolution in tumour classification, staging and optimal
45 debulking definitions (from low RD to minimal or zero RD). Histology, stage, RD and ECOG PS
46 remain reliable outcome predictors. Increasing median age at diagnosis and ECOG PS indicates
47 demographic shifts in the clinical population.

48

49 **Keywords:** ovarian cancer, survival, prognosis, diagnosis.

50 **Tweetable Abstract:** Significant improvement in ovarian carcinoma survival has been seen
51 over time. Most of this improvement is due to an extension of survival following disease
52 relapse

53

54

55 **INTRODUCTION**

56
57 With over 290, 000 new diagnoses and 180, 000 deaths per year worldwide, ovarian cancer is
58 the most lethal of all gynaecological malignancies¹. This is attributed, in part, to the high
59 frequency at which these malignancies are diagnosed at advanced stage, which represents a
60 major clinical challenge. For these advanced stage cases, the 5-year survival rate remains poor
61 at under 30%².

62
63 It is now recognised that ovarian carcinoma (OC) - which represents around 90% of ovarian
64 cancer cases - is a collection of discrete diseases, the five main histotypes of which are high
65 grade serous (HGS), endometrioid, clear cell (CC), mucinous and low grade serous (LGS) OC³.
66 These histotypes display distinct clinical characteristics, with differing intrinsic
67 chemosensitivity, typical stage at diagnosis and overall survival outcome⁴. Moreover, these
68 histotypes are now known to arise from distinct gynaecological sites⁵⁻⁹.

69
70 Despite intensive research efforts to find further therapeutic options, the standard-of-care for
71 OC has largely remained static in recent decades, comprising maximal cytoreductive debulking
72 surgery followed by platinum based chemotherapy, frequently in combination with taxanes¹⁰.
73 In recent years, the use of anti-angiogenic treatments and PARP inhibitors has been integrated
74 into routine practice, with several trials demonstrating prolonged progression-free survival
75 largely in the relapse disease setting¹¹⁻¹⁶. Recognition of the biologically distinct histotypes
76 within OC has highlighted the need for identifying new histotype-specific therapeutic
77 treatments¹⁷ and has led to rationally designed histotype-specific trials of biological agents^{18,}
78 ¹⁹.

79
80 It is well established that disease stage at diagnosis, patient age and ECOG performance status
81 (ECOG PS)²⁰⁻²³ are associated with differential survival outcomes in OC patients; moreover,
82 optimal surgical cytoreduction has emerged as one of the most important determinants of
83 outcome²⁴⁻²⁶. The definition of optimal cytoreduction has evolved alongside our
84 understanding of OC as a disease entity²⁷⁻³¹, with the goal of surgery evolving from <2cm
85 maximal dimension of the largest residual disease (RD) lesion to minimal RD (<0.5cm) to the
86 current objective of achieving no visible RD²⁹⁻³².

88 Here, we investigate the changing clinical landscape of ovarian carcinoma patients from
89 South-East Scotland (population 1.4 million) over the last 35 years (1981 – 2015) using data
90 retrieved from The Edinburgh Ovarian Cancer Database.

91 **METHODS**

92

93 **Cases**

94

95 Cases were identified using the Edinburgh Ovarian Cancer Database; patient demographics
96 and survival data, prospectively collected as part of routine clinical care, were retrieved from
97 the database. No independent ethical approval for this study was required, as determined by
98 the South East Scotland Research Ethics Service.

99

100 All pathologically confirmed epithelial OC diagnoses of serous, mucinous, endometrioid or
101 clear cell histological type between 1981-2015 were included (Figure S1), including cases
102 recorded as primary fallopian tube or primary peritoneal carcinoma, representing the vast
103 majority of OC cases in the region (for example, cases treated solely within private practice
104 will not have attended at the Edinburgh Cancer Centre). All other histotypes were excluded.
105 Historically diagnosed grade II serous carcinomas (n=189) were included with documented
106 grade III serous carcinomas (n=1010) and HGSOCS (n=554). Well differentiated serous (n=107)
107 OCs were included alongside contemporary diagnoses of LGSOC (n=10). Serous carcinomas
108 with unknown grade or variable differentiation were excluded (n=96). 51.0% of cases
109 represented either contemporary diagnoses (2010 onwards), or cases where histotype has
110 been confirmed by contemporary pathology review by an expert gynaecological pathologist
111 (CSH)³³⁻³⁹.

112

113 **Demographics**

114

115 Patients were classified into 5-year cohorts using date of pathologically confirmed OC
116 diagnosis (1981 – 1985, 1986 – 1990, 1991 – 1995, 1996 – 2000, 2001 – 2005, 2006 – 2010,
117 2011 – 2015). Staging information was based on the International Federation of Obstetrics
118 and Gynaecology (FIGO) staging system. Debulking status was classified as <2cm and ≥2cm
119 residual disease (RD). Debulking status could not be resolved beyond <2cm due to the
120 retrospective nature of these data and historic classification of <2cm RD as optimal debulking
121 prior to 2008. ECOG performance status (PS) was categorised discretely from 0 (PS 0) – 4 (PS
122 4). Due to the low number of cases with PS 4 (n=6), these cases were excluded from PS
123 analysis. 5 distinct cases were excluded from survival analysis (4 from disease-specific survival
124 (DSS) and 4 from progression-free survival (PFS) analysis) due to missing outcome data.

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Statistical analysis

DSS was evaluated as time from date of diagnosis to disease-specific death. Deaths from other causes were censored. PFS was evaluated as time from date of diagnosis to date of OC progression⁴⁰, where progression was established by radiologically confirmed progressive disease (PD), CA125 PD or clinical deterioration as determined by the treating physician. Statistical analyses were performed using R 3.6.1. Survival analyses were visualised using the Kaplan-Meier method. Survival statistics are presented with median survival with corresponding 95% confidence intervals (CIs), alongside 5- and 10-year survival rates and statistical comparison by restricted mean survival time analysis. Multivariable analyses were performed using Cox proportional hazards regression models, stratified by RD, histotype and age or PS. Differences in frequency were analysed using the Chi-squared test. $P < 0.05$ was considered statistically significant.

139 **RESULTS**

140
141 2805 patients met the inclusion criteria (Figure S1, Table 1). 51.0% of all cases represented
142 contemporary diagnoses (2010 onwards) or had their histotype confirmed by pathology
143 review: 56.5% HGS; 52.2% LGS; 42.1% endometrioid; 53.2% clear cell; 27.7% mucinous (Table
144 S1).

145
146 **Outcome of OC across all time periods**

147
148 Across the whole OC cohort, the median DSS was 3.13 years (95% CI: 2.87 - 3.42) and the
149 median PFS was 1.45 years (95% CI: 1.36 - 1.54). The overall 5-year and 10-year DSS rates were
150 38.5% (95% CI: 36.6% - 40.5%) and 27.6% (95% CI: 25.8% - 29.6%).

151
152 The current 5-year DSS, given by the 2011-2015 estimate, was 45.6% (95% CI: 40.7% - 51.1%).
153 The DSS across the year ranges, inclusive of all histotypes, increased incrementally (Figure 1,
154 Table S2), with cohorts diagnosed after 1995 demonstrating significant increases in median
155 DSS when compared to the 1981-1985 cohort. The greatest improvement was observed in the
156 most contemporary cohort patient group (diagnosed 2011-2015), with a significantly
157 increased median DSS (4.23 years, 95% CI 3.73-5.13 vs 1.73 years, 95% CI: 1.53-2.21 in 1981-
158 1985, $p < 0.0001$). Conversely, PFS across the year ranges demonstrated little improvement,
159 with no significant difference between 1981-1985 and 2011-2015 (median PFS 1.22 years, 95%
160 CI: 1.09-1.78 vs 1.58 years, 95% CI: 1.41-1.86, $p = 0.2568$) (Figure 2, Table S3). While there was
161 an apparent correlative increase in PFS with increase in DSS across time ($r = 0.80$) (Figure S2),
162 the magnitude of PFS increase was slight.

163
164 **Patterns in clinicopathological features over time**

165
166 Histotype

167 An increase in the proportion of HGSOC cases was seen (129 of 223 cases, 57.8% in 1981-1985
168 vs 373 of 544 cases, 68.6% in 2011-2015, $p < 0.0001$ across diagnosis periods) while the
169 proportion of mucinous cases decreased significantly (38 of 223 cases, 17.0% in 1981-1985 vs
170 44 of 544 cases, 8.1% in 2011-2015, $p = 0.0002$ across diagnosis periods). The proportion of
171 endometrioid cases decreased over time (23 of 223 cases, 10.3% in 1981-1985 vs 50 of 544
172 cases, 9.2% in 2011-2015, $p = 0.0005$ across diagnosis periods).

173 Stage at Diagnosis & RD following debulking

174 An overall increase in the proportion of Stage IV HGSOE patients was seen over the year
175 ranges (14 of 122 cases, 11.5% in 1981-1985 vs 85 of 317 cases, 26.8% in 2011-2015,
176 $p=0.0009$). A corresponding decrease in HGSOE patients presenting with Stage I was seen (14
177 of 122 cases, 11.4% in 1981-1985 vs 16 of 317 cases, 5.0% in 2011-2015, $p=0.0293$). The
178 proportion of cases with $<2\text{cm}$ RD increased greatly in 2011-2015 to 87.7% (vs 54.0% in 1981-
179 1985, $p<0.0001$).

180

181 ECOG Performance Status & Age at Diagnosis

182 The proportion of PS 0 cases decreased over time (73 of 173 cases, 42.2% in 1981-1985 vs 98
183 of 451 cases, 21.7% in 2011-2015, $p<0.0001$), while the proportion of PS 2 cases increased (17
184 of 173 cases, 9.8% in 1981-1985 vs 95 of 451 cases, 21.1% in 2011-2015, $p=0.0016$) (table 1).
185 The median age at diagnosis significantly increases across time (57 years in 1981-1985 vs 66
186 years in 2011-2015, $p<0.0001$) (Figure 3A). When plotted against the mean PS for each 5-year
187 cohort, a strong correlation can be observed ($r=0.86$) (Figure 3B), consistent of the overall
188 correlation between age and PS across the cohort (Figure S3).

189

190 **Associations between histological subtype and outcome**

191

192 HGSOE demonstrated the lowest 5-year DSS (25.0%, 95% CI: 22.9% - 27.2%) of the histotypes
193 (Figure 2A), while mucinous carcinomas showed the most favourable DSS (5-year survival:
194 75.0%, 95% CI: 69.9% - 80.4%, $p<0.0001$ vs HGSOE), followed by LGSOC (5-year survival:
195 63.8%, 95% CI: 55.2% - 73.8%, $p<0.0001$ vs HGSOE) and endometrioid OC (5-year survival:
196 60.0%, 95% CI: 55.1% - 65.4%, $p<0.0001$ vs HGSOE). Stage-specific analysis revealed markedly
197 poor outcome in mucinous and CC OC diagnoses at advanced stage (FIGO III/IV) (mucinous
198 median DSS: 0.88 years, 95% CI: 0.55 – 1.75, CC median DSS: 0.85 years, 95% CI: 0.65 – 1.34),
199 while LGSOC showed the highest median survival of 6.76 years in this analysis (Figure 2E).
200 Corresponding early stage (Stage I and II) DSS analysis mirrored the results of the overall DSS
201 analysis (Figure 2A).

202

203 **Associations between other clinicopathologic features and outcome**

204

205 Low RD volume following surgical debulking, lower PS and earlier stage were all associated
206 with significantly prolonged DSS (Figure 2B, 2C, 2D). Patients with $<2\text{cm}$ RD demonstrated

207 significantly higher median survival (7.33 yrs, 95% CI: 6.46 – 8.80, $p < 0.0001$) than those with
208 ≥ 2 cm of RD (1.46 years, 95% CI: 1.32 – 1.55). Each increase in performance status (reduction
209 in ECOG PS score) saw a significantly increased median survival (Figure 2D, Table S2). PS3 was
210 associated with a median survival of 0.67 years (95% CI: 0.43 – 1.01), while PS0 was associated
211 with a median survival of 5.52 years (95% CI: 4.81 – 6.80) ($p < 0.0001$, PS3 vs PS0). Similarly,
212 Stages I, II and III showed higher DSS compared to Stage IV ($p < 0.0001$ for all) (Figure 2B, Table
213 S2).

214

215 Multivariable analysis of disease stage at diagnosis, histotype, time period of diagnosis, RD
216 volume, ECOG PS and age at diagnosis reflected the univariable analyses (Table S4 and S5).
217 Notably, these data highlight an independent association of both age and PS with DSS, despite
218 the observed correlation between these two factors (Figure S3).

219

220 **Associations between clinicopathological features and outcome over time**

221

222 Changes in DSS and PFS over the 5-year time periods was investigated in the context of specific
223 clinicopathological features (Table S6, Table S7). HGSOc patients demonstrated an increase in
224 median DSS (1.56yrs, 95% CI: 1.36 – 1.92 in 1981-1985 vs 3.07yrs, 95% CI: 2.70 – 3.73 in 2011-
225 2015, $p < 0.0001$). Stage III and IV patients showed significantly prolonged median DSS from
226 1981-1985 to 2011-2015: 1.30yrs vs 3.44yrs ($p < 0.0001$) and 1.03yrs vs 2.29yrs ($p < 0.0001$)
227 respectively. Increase in median PFS was not significant in Stage III HGSOc patients (0.98yrs
228 vs 1.26yrs, $p = 0.1049$), but showed statistical significance in Stage IV HGSOc patients (0.45yrs
229 vs 1.17yrs, $p = 0.0003$). ECOG PS 1 and PS 2 patients also showed significantly prolonged
230 median DSS from 1981-1985 to 2011-2015: 1.05yrs vs 4.45yrs ($p < 0.0001$) and 0.66yrs vs
231 2.79yrs ($p < 0.0001$), respectively. Patients with < 2 cm RD displayed apparent fluctuations in PFS
232 over time, with recent years showing shorter median PFS (Table S7).

233

234 Specifically in Stage III and IV HGSOc, median DSS improved from 1981-1985 to 2011-2015:
235 1.36yrs vs 3.13yrs ($p < 0.0001$) and 1.32yrs to 2.27yrs ($p = 0.0122$) respectively (Table S8).
236 Increase in median PFS across the same period was not significant in Stage III HGSOc (0.95yrs
237 vs 1.25yrs, $p = 0.0601$) but was statistically significant in Stage IV HGSOc (0.69yrs vs 1.14yrs,
238 $p = 0.0003$) (Table S9). These data mirror the results from the pan-histotype DSS and PFS
239 analysis for stage across the cohort (Table S6, S7).

240 **DISCUSSION**

241

242 Main Findings

243 We have demonstrated and quantified the improvement in the DSS of women with epithelial
244 OC across time at the Edinburgh Cancer Centre. A similar improvement in PFS was not seen.
245 Differences in survival based on histotype, RD volume following debulking, ECOG PS and stage
246 found were consistent with previous research. An increase in advanced stage HGSOc
247 incidence and survival was seen. A strong correlation was found between increasing age at
248 diagnosis and ECOG PS across time, indicating a shift in the clinical demographic towards an
249 older patient population with more frequent co-morbidities.

250

251 Strengths and Limitations

252 Strengths of the study include the large number of cases and the high granularity of the
253 prospectively collected clinical and treatment data; few similarly extensive longitudinal
254 analyses of real-world OC data have been reported to date. Data was collected as part of
255 routine care, almost exclusively by a single individual, optimising consistency. We recognise
256 several limitations of this study. Firstly, criteria for defining progression have changed over
257 time⁴⁰, and were heterogeneous across the periods defined in our study. Our samples are
258 therefore subject to varying definitions of progression over time - including CA125 and
259 radiological evidence as well as more subjective clinical assessment. Secondly, contemporary
260 pathology review was not carried out for all cases; lack of review for all LGSOC and high grade
261 endometrioid cases, which have historically been poorly differentiated from HGSOcs, is a
262 particular weakness. Moreover, the mucinous OC group had a lower rate of pathology review
263 or contemporary diagnosis, likely a reflection of the increasing rarity of true primary mucinous
264 OC by modern pathological criteria. However, across the whole of our OC cohort, over half of
265 cases were confirmed by pathology review in previous studies or represented contemporary
266 diagnoses, in contrast to previous investigations performing no such review⁴¹⁻⁴³, representing
267 a major strength of this study over previous work. Differences in practice between treating
268 physicians and the impact of ascertainment bias also represent potential limitations.

269

270 Interpretation

271 The 5-year DSS rate observed in this study for the 2011-2015 period was 46% (95% CI: 41%-
272 51%); this is consistent with data reported by Siegel et al². A significant improvement was seen
273 from 1981-1985 where the 5-year survival rate was 31%. The median DSS improved

274 significantly from 1.73 years to 4.23 years. This improvement represents the culmination of
275 changes in management over time, including the movement toward centralised care in
276 centres with specialist expertise, more robust histopathological classification, improvements
277 in disease monitoring such as imaging technology, and the introduction of additional
278 therapeutic options. Most notably, platinum-taxane combination chemotherapy was
279 introduced as standard of care within the study time period, and there has been a paradigm
280 shift toward extensive cytoreductive surgery to maximise the chances of complete first-line
281 macroscopic resection of disease^{25,44}, aided by neoadjuvant chemotherapy in some patients.

282
283 Despite the significantly prolonged DSS observed over time, observed improvement in PFS
284 time failed to meet statistical significance (Table S3, Figure S2). This suggests that while
285 treatment has improved for recurrent disease, there has been little improvement in
286 preventing or significantly prolonging relapse. This is consistent with the static standard of
287 care for first-line OC treatment. Recent studies of first-line olaparib treatment for HGSOC
288 *BRCA1* or *BRCA2* mutant patients¹³ and hormone maintenance for LGSOC patients⁴⁵ indicate
289 that the coming years may see an improvement in OC PFS with the routine use of these agents.
290 Notably, however, these regimens will be limited to subsets of patients.

291
292 A change in proportions of different histotypes was observed over the last 35 years with
293 significant increases in HGSOC cases and decreases in mucinous and endometrioid cases. It is
294 now recognised that many previously diagnosed high grade endometrioid carcinomas in fact
295 represent variants of HGSOC⁴⁶; this may explain the relative depletion of endometrioid
296 diagnoses over time. Moreover, historic misclassification of metastatic malignancies of the
297 gastrointestinal tract as primary mucinous OC may explain the decline in mucinous cases over
298 time^{47,48}. It is therefore likely that the change in proportions of histotypes observed in this
299 study is, at least in part, a result of a refinement in classification of tumour types.

300
301 A significant increase in the proportion of HGSOC patients presenting with Stage IV disease
302 was also observed, alongside a corresponding decrease in Stage I patients. This indicates that
303 despite efforts to increase awareness of OC symptoms, these efforts have thus far failed to
304 increase the proportion of early stage diagnoses. However, median DSS for these cases has
305 increased significantly overall, and for HGSOC patients specifically (Table S9, S4), indicating
306 post-relapse management has improved. It is also feasible that the observed increased
307 incidence and survival in advanced stage cases is a consequence of the Will Rogers

308 phenomenon⁴⁹, whereby advances in diagnostic techniques (such as more sensitive imaging)
309 leads to up-staging of cases who would otherwise have been earlier stage. Certainly, increased
310 ability of contemporary imaging to detect features such as epicardial nodes could account for
311 a significant amount of stage shift over the time cohorts analysed. The improved outcome
312 observed in advanced stage cases within our study is consistent with recent SEER analysis
313 demonstrating improved outcome in this patient group⁵⁰.

314

315 The proportion of cases with <2cm of RD remained within the 50-60 % range for 1981-2010,
316 showing a large increase to 88% in the 2011-2015 year range. It is likely that the emphasis on
317 optimal debulking surgery for OC patients in recent years, driven by the recognition that
318 complete macroscopic cytoreduction is associated with markedly favourable outcome³¹, has
319 led to this increase. Moreover, this may account for decreases in median DSS and PFS seen in
320 in the <2cm RD cohort at later diagnosis periods, as modern efforts to achieve complete
321 macroscopic tumour resection – including radical debulking surgery and introduction of
322 neoadjuvant chemotherapy – has enriched this cohort for poor prognosis cases over time.

323

324 Difference in survival between histotypes observed in this study was generally consistent with
325 results of previous studies^{46, 51, 52}; LGS and endometrioid histotypes displayed better survival
326 compared to HGSOc. Peres et al.⁵² found that mucinous OC displayed favourable survival at
327 early stage, but dismal prognosis when diagnosed at advanced stage. As the majority of
328 mucinous cases were Stage I (196/282=70%), the overall trend for favourable survival seen in
329 this study, across time and within each 5-year cohort, is consistent with data previously
330 reported⁵². Our data shows that early-stage mucinous cases show favourable outcome, while
331 advanced-stage cases perform poorly. CC OC demonstrated poor survival at early stage and
332 advanced stage, consistent with previous reports of intrinsic chemoresistance in CC and
333 mucinous OC^{4, 53, 54}, highlighting the need for targeted therapies aimed at the underlying
334 biology of these malignancies.

335

336 Previous studies have uncovered and emphasised the importance of FIGO stage^{55, 56} and
337 extent of RD following debulking^{55, 57-59} as prognostic factors in OC. This study confirms the
338 importance of these two factors in OC survival, as well as ECOG PS. While there have been
339 recent reports that ECOG PS is of limited importance²⁰, we observed a clear delineation in
340 survival based on ECOG PS. Moreover, an adjusted multivariable model indicated an
341 association with survival independent of other clinicopathologic factors.

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We observed a significant increase in median patient age across time (57yrs in 1981-1985 vs 66yrs in 2011-2015, $p < 0.0001$), reflective of the UK's ageing population. A similar increase was seen on comparing the mean PS of cases across time. We show a correlation between increased ages and PS ($r = 0.86$) across time. Multivariable analysis indicated the independent adverse associations of both of these factors on survival (Table S4, Table S5). This is indicative of the shift towards an older and frailer clinical demographic, representing a clinically challenging population characterised by co-morbidities, chemotherapy delays and poorer survival outcome⁶⁰.

Collectively, these data shed new light on the shifting clinical landscape of OC management, demonstrating survival improvement across time as management of OC patients has evolved. They also highlight the current areas of greatest unmet clinical need, where new therapeutic options are urgently required to improve outcome.

357 **CONCLUSION**

358

359 OC survival in South-East Scotland has improved markedly over the last 35 years. Histology,
360 stage, extent of RD and ECOG PS are strongly associated with survival outcome. Advanced
361 stage disease has seen an increase in incidence and survival, both within HGSOC specifically
362 and across all histotypes. Despite this, PFS has not seen a corresponding increase. Recent trials
363 of first-line agents for specific subgroups of OC^{13, 45} indicate that improvement may be seen
364 over the coming years in PFS in these groups. However, in order to see a large PFS increase in
365 the overall OC population there is an urgent need for further improvements in first-line
366 management. Advanced stage CC and mucinous OCs represent those patients with greatest
367 unmet need. Moreover, the changing clinical demographic towards an older population with
368 more co-morbidities highlights a growing patient group that represent a greater clinical
369 challenge.

370 Future work should aim to investigate the impact of recently introduced therapeutic options,
371 such as anti-angiogenic therapies and PARP inhibitors, on outcome in OC. In particular,
372 whether the use of these agents in the first-line setting leads to an improvement in the
373 currently stagnant PFS of OC patients, should be investigated.

374

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377 Cancer Database, from which the clinical data used in this project were extracted. We would
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380

381 **Disclosure of Interests**

382 MM: honoraria from Tesaro, BristolMyersSquibb and Roche. FN: Non-personal interests in
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384 Novartis; honoraria/consultancy fees from Roche, AstraZeneca, Tesaro, Nucana, MSD, Clovis,
385 Foundation One, Sierra Oncology and Cor2Ed; named on issued/pending patents relating to
386 predicting treatment response in ovarian cancer beyond the scope of this work. AI, RLH, KH,
387 TR, MC, CB and CSH declare no conflicts of interest.

388

389 **Contribution to Authorship**

390 Conceptualisation: KH, CG, RLH; Data curation: TR, CB; Formal Analysis: AI, KH, RLH;
391 Methodology: AI, CG, RLH; Resources: FN, MM, CSH, CSH; Supervision: CG, RLH; Visualisation:
392 AI, Writing – original draft: AI, RLH; Writing – review & editing: AI, KH, MC, MM, FN, CSH, CG,
393 RLH.

394

395 Details of Ethics Approval

396 We have been informed by South East Scotland Research Ethics Service that studies in ovarian
397 cancer patients using data obtained as part of routine care do not require NHS ethical review.
398 As such, no independent ethical approval for this study was required.

399

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403

404

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406

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		Time period (year of diagnosis) N(%)							P-value
		1981 - 1985	1986 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2010	2011 - 2015	
Total Cases		223	275	374	470	471	448	544	
Histotype	High grade serous	129 (57.8)	153 (55.6)	203 (54.3)	295 (62.8)	315 (66.9)	285 (63.6)	373 (68.6)	P<0.001 ^a
	Clear cell	15 (6.7)	27 (9.8)	41 (11)	27 (5.7)	39 (8.3)	47 (10.5)	54 (9.9)	
	Low grade serous	18 (8.1)	14 (5.1)	10 (2.7)	18 (3.8)	17 (3.6)	17 (3.8)	23 (4.2)	
	Mucinous	38 (17)	35 (12.7)	52 (13.9)	51 (10.9)	33 (7)	43 (9.6)	44 (8.1)	
	Endometrioid	23 (10.2)	46 (16.7)	68 (18.2)	79 (16.8)	67 (14.2)	56 (12.5)	50 (9.2)	
FIGO stage at diagnosis	I	49 (22)	77 (28)	83 (22.2)	97 (20.6)	72 (15.3)	87 (19.4)	92 (16.9)	P=0.009 ^b
	II	20 (9)	30 (10.9)	41 (11)	52 (11.1)	58 (12.3)	54 (12.1)	61 (11.2)	
	III	119 (53.4)	131 (47.6)	188 (50.3)	231 (49.1)	246 (52.2)	188 (42)	232 (42.6)	
	IV	24 (10.8)	31 (11.3)	47 (12.6)	77 (16.4)	73 (15.5)	77 (17.2)	95 (17.5)	
	NA	11 (4.9)	6 (2.2)	15 (4)	13 (2.8)	22 (4.7)	42 (9.4)	64 (11.8)	
RD following debulk	<2cm	116 (52)	165 (60)	199 (53.2)	236 (50.2)	229 (48.6)	213 (47.5)	342 (62.9)	P<0.001 ^c
	≥2cm	99 (44.4)	103 (37.5)	134 (35.8)	176 (37.4)	205 (43.5)	142 (31.7)	48 (8.8)	
	NA	8 (3.6)	7 (2.5)	41 (11)	58 (12.3)	37 (7.9)	93 (20.7)	154 (28.3)	
ECOG performance status	0	73 (32.7)	112 (40.7)	83 (22.2)	102 (21.7)	79 (16.8)	52 (11.6)	98 (18)	P<0.001 ^d
	1	73 (32.7)	52 (18.9)	66 (17.6)	86 (18.3)	54 (11.5)	96 (21.4)	218 (40.1)	
	2	17 (7.6)	27 (9.8)	24 (6.4)	41 (8.7)	40 (8.5)	53 (11.8)	95 (17.5)	
	3	10 (4.5)	6 (2.2)	8 (2.1)	19 (4)	20 (4.2)	20 (4.5)	38 (7)	
	4	0 (0)	1 (0.4)	0 (0)	0 (0)	2 (0.4)	1 (0.2)	2 (0.4)	
	NA	50 (22.4)	77 (28)	193 (51.6)	222 (47.2)	276 (58.6)	226 (50.4)	93 (17.1)	
First-line chemotherapy	Single agent platinum	15 (6.7)	59 (21.5)	210 (56.1)	272 (57.9)	193 (41.0)	163 (36.4)	146 (26.8)	P<0.001 ^e
	Platinum/taxane	0 (0)	0 (0)	0 (0)	99 (21.1)	200 (42.5)	196 (43.8)	292 (53.7)	
	Other platinum combination	64 (28.7)	76 (27.6)	33 (8.8)	5 (1.1)	8 (1.7)	28 (6.3)	6 (1.1)	
	Other	65 (29.1)	63 (22.9)	47 (12.6)	1 (0.2)	2 (0.4)	0 (0)	1 (0.2)	
	None	79 (35.4)	77 (28)	84 (22.5)	93 (19.8)	68 (14.4)	61 (13.6)	99 (18.2)	
Neoadjuvant chemotherapy	No	223 (100)	275 (100)	374 (100)	470 (100)	471 (100)	368 (82.1)	333 (61.2)	P<0.001 ^h
	Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	80 (17.9) ^f	211 (38.8) ^g	

592 Table 1: Characteristics of cohort according to year of diagnosis. RD, residual disease; ECOG, Eastern Cooperative Oncology
593 Group; FIGO, International Federation of Obstetrics and Gynaecology; NA, not available. ^aChi-squared test across all
594 histotypes, 1981-1985 vs 2011-2015. ^bChi-squared test for stage IV vs stage I/II/III/, 1981-1985 vs 2011-2015. ^cChi-squared
595 test, <2cm vs ≥2cm, 1981-1985 vs 2011-2015. ^dChi-squared test, PS 0 vs 1 vs 2 vs 3/4, 1981-1985 vs 2011-2015
596 ^eChi-squared test across all regime classes, 1981-1985 vs 2011-2015. ^f35.5% of neoadjuvant cases later achieved complete
597 macroscopic resection, vs 58.8% no macroscopic residual disease in primary debulking cases. ^g32.5% of neoadjuvant cases
598 later achieved complete macroscopic resection, vs 41.7% no macroscopic residual disease in primary debulking cases. ^hChi-
599 squared test for neoadjuvant status, 1981-1985 vs 2011-2015

600

601 Figure legends

602

603 Figure 1: Survival rate by year of diagnosis. (a) Disease-specific survival (DSS) (b) Progression-free
604 survival (PFS).

605

606 Figure 2: Survival trends by (a) histotype DSS (b) stage DSS (c) debulk DSS (d) ECOG performance
607 value DSS (e) advanced stage (FIGO III/IV) histotype DSS (f) advanced stage (FIGO III/IV) histotype
608 PFS.

609

610 Figure 3: (a) Boxplot of median age at diagnosis across time.

611 (b) Scatterplot of mean ECOG performance status and mean age at diagnosis.

612

613 Figure S1: Flow diagram for case inclusion. Confirmed, confirmed by contemporary pathology
614 review; contemporary, contemporary diagnosis (2010 onwards); historic, historic diagnosis.

615

616 Figure S2: Scatterplot of median DSS and PFS increase over time. X and Y axis are in 1:1 ratio to
617 reflect relative PFS and DSS improvement.

618

619 Figure S3: Boxplot of median age at diagnosis for discrete levels of ECOG performance status.