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Clinicopathological characterization of a real-world multicenter cohort of endometrioid ovarian carcinoma: Analysis of the French national ESME-Uncancer database

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1 **Original research article**

2 **Clinicopathological characterization of a real-world multicenter cohort of endometrioid ovarian**
3 **carcinoma: analysis of the French national ESME-Uncancer database**

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63 **Keywords:** Ovarian cancer; Endometrioid; survival; prognostic factors; epidemiology.

64

65 **ABSTRACT**

66 ***Background:***

67 Prognostic significance of endometrioid epithelial ovarian cancer (EOC) is controversial. We
68 compared clinical, pathological, and biological features of patients with endometrioid and serous
69 EOC, and assessed the independent effect of histology on outcomes.

70 ***Methods:***

71 We conducted a multicenter retrospective analysis of patients with EOC selected from the French
72 Epidemiological Strategy and Medical Economics OC database between 2011 and 2016. Our main
73 objective was to compare overall survival (OS) in endometrioid and serous tumors of all grades. Our
74 second objectives were progression-free survival (PFS) and prognostic features.

75 ***Results:***

76 Out of 10263 patients included, 3180 cases with a confirmed diagnosis of serous (N=2854) or
77 endometrioid (N=326) EOC were selected. Patients with endometrioid histology were younger,
78 more often diagnosed at an early stage, with lower-grade tumors, more frequently dMMR/MSI-
79 high, and presented more personal/familial histories of Lynch syndrome-associated cancers.
80 *BRCA1/2* mutations were more frequently identified in the serous population. Endometrioid
81 patients were less likely to receive chemotherapy, with less bevacizumab. After median follow-up
82 of 51.7 months (95CI[50.1-53.6]), five-year OS rate was 81% (95CI[74-85]) in the endometrioid
83 subgroup vs. 55% (95CI[53-57] in the serous subset ($p<0.001$, log-rank test). In multivariate analyses
84 including [age, ECOG-PS, FIGO, grade, and histology], the endometrioid subtype was independently
85 associated with better OS (HR=0.38, 95CI[0.20-0.70], $p=0.002$) and PFS (HR=0.53, 95CI[0.37-0.75],
86 $p<0.001$).

87 **Conclusions:**

88 Clinicopathological features at diagnosis are not the same for endometrioid and serous EOC.

89 Endometrioid histology is an independent prognosis factor in EOC. These observations suggest the

90 endometrioid population requires dedicated clinical trials and management.

91 **INTRODUCTION**

92 Three hundred ten thousand women develop epithelial ovarian cancer (EOC) worldwide annually
93 [1]. EOC is the commonest cause of gynecological cancer-associated death in the United States, and
94 the second most common worldwide, with a 5-year overall survival rate ranging from 37% to 47%,
95 all stages combined [1,2]. EOC includes heterogeneous histologic subtypes. High-grade serous
96 carcinoma is by far the most common while endometrioid carcinoma, the second most common,
97 accounts for approximately 10% of all EOC [3]. Tumor stage, the extent of residual disease,
98 pathological subtype, and grade are the main and mostly used prognostic factors in women with
99 ovarian cancer. However, the prognostic significance of histological subtypes is controversial, given
100 the relative rarity of non-serous subtypes. Endometrioid carcinomas can be associated with
101 endometriosis [4] and have a unique molecular profile that includes significant alterations in *PTEN*,
102 *CTNNB1*, *PIK3CA*, *KMT2D*, *KMT2B*, *PIK3R1*, *ARID1A*, and *TP53*, and may display a higher frequency
103 of microsatellite instability [5–7]. Compared to serous carcinoma, endometrioid carcinomas of the
104 ovary tend to present at an earlier stage and in younger women. It is thought to have more
105 favorable outcomes than serous carcinoma of the ovary [8,9], but it remains unclear whether the
106 improved survival rates associated with endometrioid cancer are explained by the histologic
107 subtype alone, the earlier presentation, or whether other factors affect survival for this type of
108 ovarian cancer. Because of the relatively low incidence of endometrioid ovarian cancers, reports of
109 this disease often have smaller cohorts of patients, with few relevant survival data. Further analyses
110 are required to confirm if the endometrioid subtype is associated with outcome and how this
111 impact is independent of other usual prognostic criteria [10].

112 The ESME (Epidemiological Strategy and Medical Economics) Research program aims to centralize
113 existing real-world patient data in oncology [11,12]. ESME data platforms provide independent and
114 high-quality aggregated real-life data available for analysis to the scientific and medical community,

115 as well as to the pharmaceutical industry and health authorities. It compiles data from patient's
116 electronic medical records, inpatient hospitalization records, and pharmacy records. Several studies
117 have already been published related to the ESME-metastatic breast cancer database with more
118 than 22,000 patients included [13–15]. The ESME OC data platform is an electronic health records-
119 derived database populating data on consecutive patients diagnosed and/or treated (whatever the
120 stage of OC disease) between 2011 and 2017 in one of 18 French Comprehensive Cancer Centers. It
121 offers a large real-world multicenter cohort, with demographics, tumor characteristics, clinical
122 features, clinical events, and treatment-related data that may lead to a better knowledge of ovarian
123 cancer evolution. We propose in this work to explore the subset of patients with endometrioid EOC
124 included in the ESME-OC database and to compare their clinical and pathological characteristics to
125 that of patients with serous carcinoma included in the same time period.

126

127 **PATIENTS AND METHODS**

128 1. Study design and selection criteria

129 The ESME-OC database (NCT03275298) centralizes data of patients selected from 01/01/2011 until
130 12/31/2017 in one of the 18 cancer centers from the Unicancer network. Data extraction date was
131 01/06/2020. At the date of data cut-off, 10,263 patients with EOC, aged 18 or more, had been
132 included. In the present work, we selected patients diagnosed from 01/01/2011 with pathological
133 subtype documented and limited our analysis to endometrioid and serous histologies. In
134 compliance with French regulations, the ESME Ovarian Cancer database (NCT03275298) was
135 authorized by the French data protection authority (Registration ID 1976564 and authorization
136 N°DE- 2017-311). Moreover, in compliance with the applicable European regulations, a
137 complementary authorization was obtained on 14-Oct-2019 regarding the ESME research Data

138 Warehouse. No formal dedicated informed consent was required but participating centers handle
139 process to ensure that patients are informed about the re-use of their electronically recorded data.

140

141 2. Objectives of the study

142 The primary objective of this work was to explore the prognostic (overall survival) impact of the
143 endometrioid subtype in a large cohort of EOC, and to compare this prognostic value to that of
144 other known prognostic clinicopathological features, including the serous histology. Secondary
145 objectives were to explore the correlation between pathological subtypes and progression-free
146 survival and to assess prognostic features within the endometrioid population.

147

148 3. Data collection and statistical analysis

149 The level of statistical significance was set at $\alpha=0.05$. All tests will be two-sided. Statistical analyses
150 were performed with the SAS® 9.4 software. Categorical variables were described using counts and
151 frequencies (computed based on available data for the considered criterion), and quantitative
152 variables were described using medians and ranges. An arbitrary 50-years cutoff was also used to
153 dichotomize the age variable, as it can be considered as a surrogate for menopausal status.
154 Patients' characteristics between endometrioid and serous tumors arm were compared using Chi-
155 square or exact Fisher's tests for qualitative variables, and rank-Wilcoxon's tests for quantitative
156 variables.

157 Follow-up was measured from the date of diagnosis to the date of last news for live patients.

158 Progression-free survival (PFS) was defined from the date of diagnosis to the date of progression.

159 PFS events were relapse in case of complete remission after the first therapeutic sequence,

160 progression in absence of complete remission, diagnosis of a metachronous neoplasm, or death in

161 absence of relapse or progression at the date of the last news. Overall survival (OS) was calculated

162 from the date of diagnosis to the date of death, whatever the cause.

163 We explored the prognostic impact of the main prognostic features: age, ECOG (Eastern
164 Cooperative Oncology Group) performance status, FIGO (International Federation of Gynecology
165 and Obstetrics) stage, grade, and complete cytoreductive surgery achievement. Concerning tumor
166 grade, serous tumors were classified using the WHO (World Health Organization) classification (high
167 vs. low). Endometrioid tumors were classified into three sub-categories: 1, 2, and 3. Grade 1 and 2
168 were gathered in a “low-grade” category and grade 3 tumors were called “high-grade
169 endometrioid” to be compared to the two-group classification of serous tumors. We also analyzed
170 biological features such as the presence of *BRCA1/2* mutations and mismatch repair deficiency
171 (dMMR, defined by immunohistochemistry) and/or microsatellite instability (MSI-high, defined
172 using specific PCR assays). *BRCA1/2* and dMMR/MSI-high status were retrospectively retrieved
173 from clinical files. We also analyzed the impact on the outcome of chemotherapy regimen. The
174 correlation of these parameters to the outcome was assessed by the Cox regression method in both
175 univariate and multivariate analyses. Multivariate analyses included only pre-therapeutic variables
176 with $p < 5\%$ in univariate analysis and less than 30% of missing data.

177 Hazard ratios were provided with their Wald’s bilateral confidence intervals (CI) and tests p -values
178 for significance. Follow-ups were estimated using the reverse Kaplan–Meier’s method. Patients lost
179 to follow-up or without event were right-censored at the date of their last follow-up. Survival
180 curves were estimated using the Kaplan–Meier’s method and the median PFS and OS were
181 calculated with their bilateral confidence intervals.

182 This study was conducted in compliance with the STROBE (Strengthening the Reporting of
183 Observational Studies in Epidemiology) criteria (see Supplementary checklist) [16].

184

185 **RESULTS**

186 1. Population demographics

187 Out of the 10,263 patients included in the ESME-OC database, we identified 2,854 serous EOC and
188 326 endometrioid EOC diagnosed from 01/01/2011 until 12/31/2016, for a whole population of
189 3180 patients (Figure S1).

190 Demographics are detailed in Table 1. The median age at diagnosis was 63.3 years. Most of the
191 patients had a good performance status (86.4% PS 0-1). FIGO stage III was the more frequent
192 (65.7%) with 24.5% of stage I-II tumors. Eighty percent were high-grade tumors. A minority of the
193 patients (13.7%) had a personal history of cancer prior to EOC diagnosis, including 302 breast
194 cancers and 44 Lynch syndrome-associated cancers. Data concerning cancer family history was
195 available for 2423 patients, including a quarter (26.7%) with a family history of breast and/or
196 ovarian cancer. *BRCA1/2* deleterious mutations were identified for 24% of the patients with data
197 available. dMMR/MSI-high status was identified for 5.8% of the cases for which it was explored.

198 More than 80% (83.5%) had a complete cytoreductive surgery whether in the front-line or interval
199 setting. More than 90% of the patients received systemic chemotherapy in the first-line setting,
200 mainly with a platinum-taxane doublet.

201

202 2. Clinicopathological discrepancies between serous and endometrioid cancers (Table 1)

203 Patients with endometrioid EOC were younger with 27.6% of patients under 50. They were more
204 likely to be diagnosed with morbid obesity (18.8%). Endometrioid cases were often diagnosed at an
205 early stage (68.5% FIGO I-II, vs. 18.9% for serous cases, $p<0.001$). Low-grade tumors were also more
206 frequent in this subtype (68.7% grade 1-2 endometrioid EOC vs. 14.3% low-grade serous EOC,
207 $p<0.001$). Among the patients with data available, history of Lynch syndrome-associated cancer was

208 more frequent for endometrioid tumors (3.8% vs. 1.2%, $p=0.001$). As shown in Figure 1, there were
209 more *BRCA* mutated cases in the serous population. However, this was significant only for *BRCA1*.
210 Even though data were scarce concerning this point, endometrioid cases were more often
211 dMMR/MSI-high than serous cancers (Odds ratio =6.83, 95CI [2.8-16.64], $p<0.0001$).
212 Endometrioid cases were less likely to receive chemotherapy ($p<0.001$) with less bevacizumab use
213 ($p<0.001$), and there was a trend to a higher rate of complete cytoreductive surgery in this
214 population (90.1% vs. 83.0%, $p=0.08$).

215

216 3. Overall survival analysis

217 After a median follow-up of 51.7 months (95CI [50.1-53.6]), median OS was 72.8 months (95CI
218 [67.5-74.6]), with a 5y-OS rate of 58% [55%-60%] for the whole population. OS univariate Cox
219 regression analysis identified age at diagnosis over 50 (HR=1.74 (95CI [1.43-2.11]); $p<0.001$), ECOG
220 PS 2 (HR=2.03 [1.69-2.44]; $p<0.001$) and ECOG PS 3-4 (HR=3.35 [2.49-4.49]; $p<0.001$), FIGO III-IV
221 (HR=5.37 [4.00-7.19]; $p<0.001$), high grade (HR=1.50 [1.23-1.82]; $p<0.001$), and residual disease
222 after cytoreductive surgery (HR=2.33 [1.88-2.90]; $p<0.001$), as negatively associated with OS (Table
223 2). *BRCA1/2* mutation was associated with better survival. Endometrioid histological subtype was
224 associated with better OS compared to serous (HR=0.36 [0.27-0.48], $p<0.001$), and 5-year OS was
225 81% [74%-85%] in endometrioid subgroup vs. 55% [53%-57%] for patients with serous ovarian
226 cancer (Figure 2). In a multivariate analysis including age at diagnosis, ECOG PS, FIGO stage, grade,
227 and histology, the endometrioid subtype remained an independent positive OS-prognostic factor
228 (HR=0.38 [0.20-0.70]; $p=0.002$), as well as young age, good ECOG PS, and early FIGO stage (Table 2).
229 To confirm the prognostic value of the endometrioid subtype whatever the grade, we explored OS
230 according to histotype in both low-grade and high-grade tumors. Endometrioid EOC displayed a

231 better OS in both subgroups (Figure S2). Five-year OS was 89% for low-grade endometrioid
232 carcinoma vs. 60% for low-grade serous tumors ($p<0.001$), and 76% for high-grade endometrioid vs.
233 55% for high-grade serous EOC ($p=0.003$), respectively.

234 When considering the endometrioid subtype only, OS univariate analysis identified age, FIGO stage,
235 grade, and *BRCA* status, as significant prognostic features (Figure 3). Within the endometrioid
236 subtype, *BRCA* mutations were associated with worse survival (HR=0.30 [0.11-0.82], in favor of
237 cases without deleterious mutation).

238

239 4. Progression-free survival analysis

240 Median PFS was 10.2 months (95CI [9.1-11.5]) for the whole population, with a 5y-PFS rate of 20%
241 [19%-22%]. Age, ECOG PS, FIGO stage, grade, achievement of complete cytoreductive surgery, and
242 dMMR were significantly associated with PFS in univariate analysis (Table 3). As observed for OS,
243 endometrioid tumors were associated with better 5y-PFS (55% vs. 16% for serous cases; HR=0.33,
244 95CI [0.28-0.40]; $p<0.001$) (Figure 4). Endometrioid histology, as well as ECOG PS and FIGO stage,
245 remained independently associated with PFS in multivariate analysis (Table 3).

246 When considering the endometrioid subtype only, the univariate analysis identified age, FIGO
247 stage, cytoreductive surgery status, grade, and *BRCA* status as significantly associated with PFS
248 (Figure 5). Bevacizumab administration was associated with a poorer PFS probably because it was
249 used for tumors with the highest risk of relapse. *BRCA* mutations were associated with a worse PFS.
250 The higher incidence of *BRCA* mutations in high-grade tumors may have contributed to this lack of
251 protective effect of *BRCA* mutations. Eight of 13 (62%) patients with *BRCA1/2* mutations and grade
252 available had high-grade tumors vs. 38% of low-grade cases. However, due to the low number of

253 events in this population, we were not able to perform multivariate analyses for this subset and to
254 explore the independent prognostic value of *BRCA* status.

255

256

257 **DISCUSSION**

258 The present analysis of the French national ESME-OC Unicancer database confirmed that women
259 with endometrioid ovarian cancer were younger and had earlier stage tumors compared to women
260 with serous ovarian cancer. They were less likely to display *BRCA1/2* mutations but their tumors
261 were more frequently DNA mismatch repair deficient. Endometrioid subtype was correlated to
262 better overall and progression-free survivals, irrespectively of age, stage, grade, and ECOG PS.
263 Within the endometrioid subtype, we identified older age at diagnosis, advanced FIGO stage, high
264 pathological grade, and *BRCA* mutations, as significant poor prognostic features.

265 Previously published data on histotype-specific survival have been contradictory and presented
266 some limitations. Most of the studies were published prior to the 2014 WHO guidelines and did not
267 systematically reflect current knowledge of ovarian cancer pathogenesis [17–27]. More recent
268 studies have indicated at least a number of features suggestively associated with long-term
269 outcomes, including earlier age at diagnosis, earlier stage disease, absence of residual disease after
270 cytoreductive surgery, non-serous histologies, and lower CA-125 levels [28–31]. This has led the
271 ESMO/ESGO guidelines to consider adjuvant chemotherapy as optional for grade 1-2 stage IB/IC
272 endometrioid tumors [32]. Our data support these clinical observations including the fact that the
273 patients included in our study underwent more complete cytoreductive surgeries and received less
274 platinum-based chemotherapy and bevacizumab. In a 2019 analysis of SEER data limited to low-

275 grade endometrioid tumors [9], Peres *et al.* examined survival patterns after ovarian cancer in
276 relation to its histologic subtypes, grade, and stage. Consistently with our results, endometrioid
277 cancers were diagnosed at younger age and less commonly at distant stage in comparison with
278 high-grade serous cancers. Irrespectively of stage, the best survival outcomes were also observed in
279 endometrioid subtype. Currently, SEER does not capture information about adjunctive
280 immunohistochemistry or genomic markers increasingly used in surgical pathology laboratories and
281 does not have data on additional prognostic factors (ECOG PS, BMI, history of familial cancer...). Our
282 study identified more frequent history of Lynch syndrome-associated cancer, and mismatch repair
283 deficiency or high-level microsatellite instability in endometrioid subtype compared to serous.
284 Women with Lynch syndrome present an increased risk of developing ovarian cancer, estimated at
285 7-12% [33–35]. These malignancies are primarily non-serous, and the majority are clear cell or
286 endometrioid [36,37]. Reciprocally, a recent study identified germline pathogenic or likely
287 pathogenic variants confirming Lynch syndrome in more than 65% of patients with dMMR ovarian
288 cancer by immunohistochemistry [38]. Identification of dMMR/MSI-high as a biomarker for
289 response to immune checkpoint blockade represents a breakthrough in the treatment of
290 individuals with advanced solid tumors [39,40], including endometrioid endometrial cancer [41].
291 However, it is unlikely to explain the increased survival rates of the endometrioid patients included
292 in this cohort, with regard to the inclusion dates (2011 to 2017). Data of immune checkpoint
293 inhibitors' efficacy on dMMR endometrioid EOC would be of interest to tailor the treatment of this
294 subtype. In the first report from the prospective Lynch syndrome database [42], Møller *et al.*
295 described very good survival outcomes after first ovarian cancer in patients receiving colonoscopy
296 and gynecological surveillance. Thus, family planning and cancer surveillance might also play a role
297 in the more favorable outcomes of endometrioid ovarian cancer compared to serous subtype.

298 Our work had some limitations. First, its retrospective design may have induced some recruitment,
299 information, and treatment biases. However, the fact that patients were included in several
300 reference cancer centers with homogeneous treatment guidelines limits these biases. Moreover,
301 our short period of inclusion (2011-2016 vs. 2004-2014 for the SEER study [9]) reduces potential
302 biases associated with treatment guidelines modifications over time. Second, very few of our
303 patients received PARP inhibitors, a gold standard for ovarian cancer treatment for homologous
304 recombination deficient tumors treated in the first-line setting and for platinum-sensitive recurrent
305 tumors [43–48]. However, only a very small part (0 to 5%) of the patients included in pivotal
306 randomized trials assessing PARP inhibitors efficacy had endometrioid cancer. PARP inhibitors
307 benefits in this population are thus still unknown. Moreover, the rates of *BRCA1/2* mutations and
308 homologous recombination deficiency remain unclear in this subset. We observed in the present
309 work that more than 14% of endometrioid tumors harbor *BRCA1/2* mutations, which is less than for
310 serous tumors but remains clinically significant. As the ESME research program is dedicated to
311 clinical data hosted in the ESME Data Warehouse, no formalin-fixed paraffin-embedded sample is
312 available via the ESME-OC database. We were thus not able to complete molecular analyses for all
313 the patients included and to add HRD assays that were not routinely performed during the
314 selection period. This also could have allowed comprehensive MMR and PD-L1 evaluation, which
315 would have been of interest for endometrioid tumors. There was no central pathology review;
316 nevertheless, the patient population was collected from reference comprehensive cancer centers,
317 and the tumor characteristics were analyzed by highly qualified and national expert pathologists.
318 Finally, as endometrioid EOC are known to be associated with endometriosis [49], knowledge of the
319 history of endometriosis would have allowed us to compare endometriosis-associated
320 endometrioid EOC to other tumors, both in terms of molecular alterations and survival.

321 Endometriosis could also have induced closer gynecological monitoring and thus may have
322 explained that endometrioid EOC is diagnosed at an earlier stage.

323 In conclusion, clinicopathological features at diagnosis are not the same for endometrioid and
324 serous EOC. Endometrioid histology is an independent prognosis factor in EOC, irrespective of other
325 usual prognostic features. Histotype-specific survival patterns are likely a result of differences in
326 tumor biology and treatment effectiveness suggesting the endometrioid population requires
327 dedicated clinical trials. The management of ovarian cancer, as well as surveillance and familial
328 counseling, need to evolve from a one-size-fits-all approach to more of a histotype-specific
329 approach.

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492

493 **FIGURES CAPTIONS**

494 Figure 1: Prevalence of pathogenic alterations in ovarian cancer as per the pathological subtype. *

495 $p < 0.05$, Chi-2 test

496 Figure 2: Kaplan Meier curves for overall survival (OS) depending on the pathological subtype. $P =$

497 Log-rank p -value.

498 Figure 3: Forest plots for overall survival (OS) univariate analyses within endometrioid ovarian

499 cancer patients. $P =$ Wald's test p -value.

500 Figure 4: Kaplan Meier curves for progression-free survival (PFS) depending on the pathological

501 subtype. $P =$ Log-rank p -value.

502 Figure 5: Forest plots for progression-free survival (PFS) univariate analyses within endometrioid

503 ovarian cancer patients. $P =$ Wald's test p -value.

504

505 **COMPLIANCE WITH ETHICAL STANDARDS**

506 **Conflict of interest:** All the authors declare that they have no conflicts of interest to disclose related

507 to this work.

508 **Ethics approval:** In compliance with French regulations, the ESME Ovarian Cancer database

509 (NCT03275298) was authorized by the French data protection authority (Registration ID 1976564

510 and authorization N°DE- 2017-311). Moreover, in compliance with the applicable European

511 regulations, a complementary authorization was obtained on 14-Oct-2019 regarding the ESME

512 research Data Warehouse. No formal dedicated informed consent was required but participating

513 centers handle process to ensure that patients are informed about the re-use of their electronically
514 recorded data.

515 **Authors' contributions:** Alexandre de Nonneville, Renaud Sabatier: Conceptualization, Formal
516 analysis, Methodology, Resources, Validation, Roles/Writing - original draft; Writing - review &
517 editing. Christophe Zemmour: Formal analysis, Methodology, Visualization, Writing - review &
518 editing. Coralie Courtinard, Gaëtane Simon: Project administration. All other authors: Resources,
519 Writing - review & editing.

520

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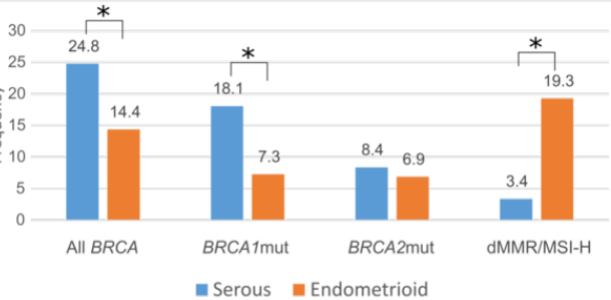
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548 *Unicancer local coordinators:*

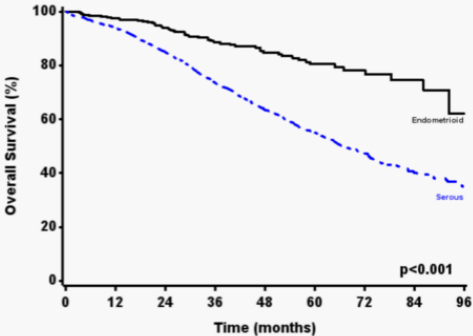
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553

Frequency



Overall Survival - Histological type



Endometrioid

326

294

257

189

141

95

54

26

2

Serous

2854

2553

2168

1523

1010

614

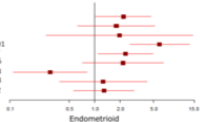
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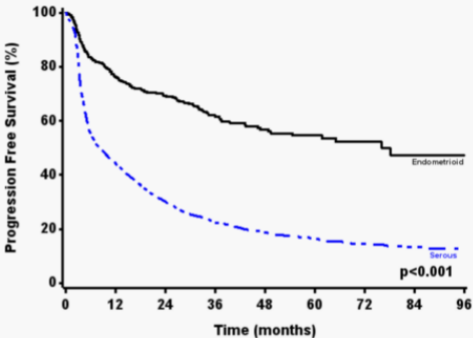
19

Overall survival univariate analysis

	N	HR [95% CI]	p
Age at diagnosis, years, ≥50 vs <50	326	2.19 [1.03-4.67]	0.042
ECOG PS 2 vs 0-1	180	1.81 [0.63-5.17]	0.267
ECOG PS 3-4 vs 0-1		1.98 [0.27-14.54]	0.504
FIGO stage III-IV vs I-II	251	5.87 [2.63-13.12]	<0.001
Grade high vs low	227	2.32 [1.10-4.90]	0.027
Complete cytoreductive surgery, no vs yes	91	2.17 [0.72-6.53]	0.166
BRCA deleterious mutation, no vs yes	139	0.30 [0.11-0.82]	0.018
Chemotherapy, platinum-taxanes doublet vs platinum monotherapy	326	0.79 [0.24-2.59]	0.698
Chemotherapy, platinum-taxanes doublet vs bevacizumab triplet		1.30 [0.57-2.93]	0.532



Progression Free Survival - Histological type



Endometrioid
Serous

326	231	190	128	88	57	26	12	1
2854	1208	774	462	303	188	96	30	0

Progression-free survival univariate analysis

	N	HR [95% CI]	p
Age at diagnosis, years, ≥ 50 vs < 50	326	1.79 [1.16-2.76]	0.008
ECOG PS 2 vs 0-1	180	2.74 [1.40-5.34]	0.003
ECOG PS 3-4 vs 0-1		2.59 [0.63-10.63]	0.186
FIGO stage III-IV vs I-II	251	5.29 [3.44-8.14]	< 0.001
Grade high vs low	227	2.02 [1.29-3.16]	0.002
Complete cytoreductive surgery, no vs yes	91	2.32 [1.03-5.22]	0.043
BRCA deleterious mutation, no vs yes	139	0.43 [0.23-0.79]	0.007
Chemotherapy, platinum monotherapy vs platinum-taxanes doublet	326	1.02 [0.47-2.22]	0.952
Chemotherapy, bevacizumab triplet vs platinum-taxanes doublet		1.98 [1.23-3.35]	0.006

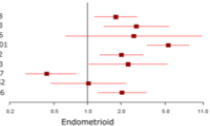


Table 1. Demographics on the whole population and comparison across histologies. Data are notified as N (% of cases with data available)

Clinical features at diagnosis		All (N=3180)	Serous	Endometrioid	p-value
Age at diagnosis, years (median, min-max)		63.3 (16.8-90.9)	63.8 (16.8-90.9)	59.4 (24.1-86.8)	<0.0001
Age at diagnosis ≤ 50 years		458 (14.4)	368 (12.9)	90 (27.6)	<0.0001
Body mass index ≥ 30		353 (13.5)	305 (12.9)	48 (18.8)	0.009
ECOG performance status	0-1	1986 (86.4)	1821 (86.0)	165 (91.7)	0.099
	2	241 (10.5)	229 (10.8)	12 (6.7)	
	3-4	71 (3.1)	68 (3.2)	3 (1.7)	
History of breast cancer		302 (9.9)	280 (10.3)	22 (7.0)	0.071
History of Lynch syndrom associated cancer		44 (1.4)	32 (1.2)	12 (3.8)	0.001
FIGO stage	I	350 (15.7)	213 (10.8)	137 (54.6)	<0.0001
	II	195 (8.8)	160 (8.1)	35 (13.9)	
	III	1463 (65.7)	1390 (70.4)	73 (29.1)	
	IV	218 (9.8)	212 (10.7)	6 (2.4)	
Pathological, molecular, and biological features at diagnosis					
Grade	low	444 (19.9)	288 (14.3)	156 (68.7)	<0.0001
	high	1791 (80.1)	1720 (85.7)	71 (31.3)	
BRCA deleterious mutation	all	448 (24.0)	428 (24.8)	20 (14.4)	0.008
	BRCA1	311 (17.3)	301 (18.1)	10 (7.3)	0.002
	BRCA2	145 (8.3)	135 (8.4)	10 (6.9)	0.54
dMMR/MSI-high		22 (5.8)	11 (3.4)	11 (19.3)	<0.0001
CA 125, U/ml (median, min-max)		240 (2-162849)	278 (2-162849)	63 (2-7893)	<0.0001
Treatments received					
Complete cytoreductive surgery		984 (83.5)	902 (83.0)	82 (90.1)	0.078
First line treatment	platinum monotherapy	149 (4.7)	132 (4.6)	17 (5.2)	<0.0001
	platinum-taxane	2147 (67.5)	1945 (68.2)	202 (62.0)	
	platinum-taxane-bevacizumab	633 (19.9)	604 (21.2)	29 (8.9)	
	other	16 (0.5)	14 (0.5)	2 (0.6)	
	no systemic treatment	235 (7.4)	159 (5.6)	76 (23.3)	

PS: performance status; dMMR: mismatch repair deficiency; MSI: microsatellite instability

unless otherwise specified

Table 2. Cox regression overall survival analysis

		Univariate analysis			Multivariate analysis (<i>N</i> =1251)	
		<i>N</i>	Hazard Ratio [95CI]	<i>p</i> -value	Hazard Ratio [95CI]	<i>p</i> -value
Age at inclusion, years	≥50 vs <50	3180	1.74 [1.43-2.11]	<0.001	1.36 [1.03-1.80]	0.029
ECOG PS	2 vs 0-1	2298	2.03 [1.69-2.44]	<0.001	1.40 [1.05-1.87]	0.021
	3-4 vs 0-1		3.35 [2.49-4.49]			
FIGO stage	III-IV vs I-II	2226	5.37 [4.00-7.19]	<0.001	3.80 [2.61-5.52]	<0.001
Grade	high vs low	2235	1.50 [1.23-1.82]	<0.001	0.90 [0.69-1.17]	0.433
Histology	endometrioid vs serous	3180	0.36 [0.27-0.48]	<0.001	0.38 [0.20-0.70]	0.002
Complete cytoreductive surgery	no vs yes	1178	2.33 [1.88-2.90]	<0.001		
<i>BRCA</i> deleterious mutation	no vs yes	1867	1.87 [1.49-2.33]	<0.001		
dMMR/MSI-high	no vs yes	382	1.52 [0.56-4.15]	0.42		
Chemotherapy regimen	platinum monotherapy vs platinum-taxane doublet	3180	1.89 [1.46-2.45]	<0.001		
	bevacizumab triplet vs platinum-taxane doublet		1.11 [0.96-1.28]			

PS: performance status; dMMR: mismatch repair deficiency; MSI: microsatellite instability
Features with more than 30% of missing data were not included in multivariate analysis

Table 3. Cox regression progression-free survival analysis

		Univariate analysis			Multivariate analysis (N =1251)	
		N	Hazard Ratio [95CI]	p-value	Hazard Ratio [95CI]	p-value
Age at inclusion, years	≥50 vs <50	3180	1.40 [1.24-1.58]	<0.001	0.92 [0.77-1.11]	0.391
ECOG PS	2 vs 0-1	2298	1.53 [1.32-1.76]	<0.001	1.33 [1.08-1.64]	0.007
	3-4 vs 0-1		1.87 [1.45-2.40]	<0.001	1.87 [1.23-2.83]	0.003
FIGO stage	III-IV vs I-II	2226	4.60 [3.94-5.37]	<0.001	3.76 [3.02-4.68]	<0.001
Grade	high vs low	2235	1.64 [1.43-1.87]	<0.001	1.10 [0.91-1.33]	0.318
Histology	endometrioid vs serous	3180	0.33 [0.28-0.40]	<0.001	0.53 [0.37-0.75]	<0.001
Complete cytoreductive surgery	no vs yes	1178	1.59 [1.35-1.88]	<0.001		
BRCA deleterious mutation	no vs yes	1867	1.13 [1.00-1.27]	0.055		
dMMR/MSI-high	no vs yes	382	2.13 [1.13-4.00]	0.019		
Chemotherapy regimen	platinum monotherapy vs platinum-taxane doublet	3180	0.89 [0.73-1.09]	0.25		
	bevacizumab triplet vs platinum-taxane doublet		1.11 [1.01-1.23]	0.038		

PS: performance status; dMMR: mismatch repair deficiency; MSI: microsatellite instability

Features with more than 30% of missing data were not included in multivariate analysis