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Long term follow-up of a large series of stage-II/III atypical proliferative serous ovarian tumors

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4 **LONG TERM FOLLOW-UP OF A LARGE SERIES OF STAGE-**
5 **II/III ATYPICAL PROLIFERATIVE SEROUS OVARIAN**
6 **TUMORS**

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16 **Running title: Stage II/III atypical proliferative serous ovarian tumors.**

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Stage II/III Atypical proliferative serous ovarian tumors.

44 **Abstract**

45 **Background:** The aim of this study was to assess prognostic factors and implications on further
46 management in a large series of stage-II or III Atypical Proliferative Serous Tumors (APST) with
47 a long-term follow-up.

48 **Patients and Methods:** Patients with APSTs and peritoneal implants treated in, or referred to, our
49 institution were retrospectively reviewed. Prognostic factors on invasive recurrence, disease-free
50 (DFS) and overall survival (OS) were analyzed.

51 **Results:** Between 1971 and 2017, 212 patients were identified and followed (33 having invasive
52 implants). After a median follow-up of 115 months, 70 recurrences were observed, 28 of them
53 under the form of invasive disease. DFS at 5 years and 10 years was 73% and 62% respectively.
54 The use of a conservative treatment (HR=5.5[3.33-9.08], $p<.0001$), the presence of ≥ 3
55 peritoneal sites with implants (HR=1.65[1.01-2.72], $p=.045$) were unfavorable prognostic factors
56 for DFS. The presence of ≥ 3 peritoneal sites with implants (HR=3.02[0.96-9.53], $p=.049$) and
57 the presence of stromal microinvasion (HR=3.19[1.12-9.1], $p=.022$) were unfavorable prognostic
58 factors for OS. Non-conservative surgery (HR=7[2.35-20.87], $p=0.0002$), invasive implants
59 (HR=5.37[1.29-22.26], $p=0.013$), and ≥ 3 peritoneal sites with implants (HR=3.56 [1.11-11.39],
60 $p=0.024$) were identified as predictors of recurrence in the form of an invasive disease. Invasive
61 implants were not associated with DFS (HR=1.39[0.77-2.51], $p=0.27$), nor OS (HR=1.76[0.57-
62 5.47], $p=0.32$).

63 **Conclusion:** After a long-term follow-up, type of peritoneal implants is no longer a prognostic
64 factor for OS. Implants ≥ 3 peritoneal sites seem to impact significantly OS and then require a
65 specific follow-up in this subgroup of patients.

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70 **Key words:** Atypical Proliferative Serous Tumour, ovary, invasive implants, noninvasive
71 implants, extraovarian low-grade serous carcinoma.

72 **Introduction**

73 Taylor described low malignant potential ovarian tumors for the first time in 1929[1].
74 This ovarian disease is defined as lacking overt stromal invasion at histological examination; it is
75 characterized by a less aggressive behavior than invasive epithelial ovarian tumors [1]. The two
76 main histological groups are mucinous and serous borderline tumors, the latter being the most
77 frequent in Europe and North America [2]. Unlike mucinous diseases, serous borderline tumors
78 are bilateral in 15% to 25% and associated to extraovarian diseases in 25% to 35% in the form of
79 “implants” [3-6]. During 3 decades, peritoneal implants were divided in noninvasive (exhibiting
80 no evidence of "destructive stromal" invasion) and invasive (showing invasion of the underlying
81 tissue or solid nests), with the morphological aspects being very close to those observed in
82 patients with peritoneal carcinomatosis from low grade serous carcinoma (LGSC). In 2014, the
83 classification of gynecological tumors has been revised, calling the “previous” serous “borderline
84 tumors” (or “low malignant potential”) “Atypical Proliferative Serous Tumors” (APST)[9].
85 Noninvasive implants are so called, because “implants”, and invasive implants are now
86 considered as extraovarian LGSC [9]. To simplify the wording of pathologic patterns in this
87 paper (which is a crucial aspect), phrasing of the WHO 2014 classification will be used in
88 brackets after the use of the “most” conventional (or historical) terms.

89 The previous characterization between both implants had been considered as strategically
90 and therapeutically the most important issue in stage-II or III APSTs. Anyhow, the crucial
91 therapeutic step is the removal of all peritoneal implants, with surgery being then the exclusive
92 treatment in patients with noninvasive implants (implants)[10,11]. During the last three decades,
93 adjuvant treatment was considered in patients with invasive implants [6,12]. Nevertheless, as we
94 had no level A evidence of the efficacy of chemotherapy in this context, surgical resection
95 (without adjuvant treatment) is now considered to be the standard management in patients with
96 invasive implants (extraovarian LGSC)[11]. But the prognosis and outcome of patients with

97 peritoneal spread continue to fuel debate, particularly in respect of both subgroups of peritoneal
98 disease [6,13-16]. The real evaluation of the impact on overall survival (OS) of both subtypes of
99 implants is difficult, because the frequency of patients with invasive implants (extraovarian
100 LGSC) is lower. Furthermore, the rate of events potentially impacting the survival (recurrences
101 in the form of invasive disease or carcinoma) is not so frequent, even in stage-II/III APSTs; this
102 is why, a very long-term follow-up is required (> 5 years) to screen possible late recurrences; so,
103 most retrospective studies (that are, by definition, retrospective in these rare tumors) lack power
104 to have a clear idea to screen the real impact on OS of noninvasive implants (implants) or
105 invasive implants (extraovarian LGSC)[6]. Our aim in this study of the largest series of patients
106 with advanced-stage APST and a median follow-up duration > 5 years is to determine the
107 prognosis of patients on OS and then potential implications on further management or follow-up
108 strategies.

109

110 *Patients and Methods*

111 From 1971 to 2017, 231 patients treated in/or referred to our institution for an APST with
112 peritoneal implants had their histologic slides reviewed by the same pathologist in our center.
113 APSTs were defined as an ovarian tumor with: 1) a stratified epithelial lining; 2) the formation
114 of microscopic papillary projections; 3) nuclear atypia, and 4) the absence of frank stromal
115 invasion [5]. The micropapillary patterns (noninvasive LGSC), stromal microinvasion
116 (microinvasive carcinoma and micropapillary pattern (noninvasive LGSC) were evaluated
117 according to the 2014 WHO classification [9]. Stromal microinvasion (microinvasive carcinoma)
118 could be observed on the ovarian tumor and was then defined as deep invasion < 5 mm [9].

119 Patients were included in the current analysis if the follow-up duration was greater than
120 12 months. An Institutional Review Board Agreement was obtained for this study.

121 The staging classification used was the 2014 FIGO classification.¹⁷ The tumor stage was
122 recorded using the macroscopic description during the surgical procedure and by reviewing the
123 pathology records. Morphology of peritoneal implants was classified as noninvasive (implants)
124 or invasive (extraovarian LGSC), according to the criteria previously described by Bell and
125 Scully and the recent WHO classification [7-9].

126 Surgery consisted in either non-conservative (bilateral salpingo-oophorectomy with or
127 without hysterectomy), or conservative treatment (defined as conservation of the uterus and
128 salvaging of at least a portion of one ovary). Additional staging surgical procedures were
129 occasionally performed. This was simultaneously dependent on:
130 -the surgical teams;
131 -whether the tumor was diagnosed during or after the surgical procedure;
132 -the disease expansion. Patients had undergone either a laparotomic or a laparoscopic approach
133 performed during a one-step surgical procedure, if the diagnosis was made using a frozen section
134 analysis during the operation, or during restaging surgery.

135 Adjuvant treatment (chemotherapy, external radiation therapy, and chemotherapy with
136 external radiation therapy) was administered until 1985. The indications for adjuvant treatment
137 and its specific type depended on three factors:
138 -the pathologic results (characteristics of peritoneal implants);
139 -the persistent residual tumor; and
140 -the date treatment was administered.

141

142 Two endpoints were retained for the statistical analysis:
143 -the rate of recurrence in the form of invasive disease (invasive implants/extraovarian LGSC,
144 LGSC or psammocarcinoma);

145 –the survival (OS and Disease Free Survival/DFS).

146

147 *Statistical Analyses*

148 Quantitative variables are described as the mean (+/- standard deviation (SD) and
149 compared with Student's t-test or as median (Inter Quartile Range (IQR)) depending on the
150 assumption of normality. Qualitative variables are described as count (percentage) and compared
151 with Chi² test or Fisher's exact test as appropriate.

152 Overall survival was defined as the time between the date of surgery and death of any
153 cause, while disease-free survival was defined as the time from surgery to recurrence and death
154 from any cause, whichever came first. Survival curves were calculated according to Kaplan-
155 Meier method and compared with the log-rank test.

156 For the prognosis analysis, a single variable Cox Proportional Hazard (Cox PH) model
157 was used, and results are presented as Hazard Ratio (HR) with their 95% confidence interval.
158 Any variable with a p-value lower than .1 was subsequently entered in a multivariable Cox PH
159 model with backward variable selection based on Akaike's Information Criterion (AIC).

160 All tests are 2-tailed and a p-value of .05 was chosen to denote statistical significance. All
161 analyses were done with the R 3.15 software (The R Core Team, Vienna, Austria).

162

163 *Results*

164 Among 231 consecutive patients initially referred to the study, 19 were excluded (due to
165 the occurrence of carcinoma during pathologic review in 5 patients, and a lack of sufficient
166 follow-up in 14 others). The median age of the 212 included patients at the time of surgery was
167 35 years (range, 14-74). Details about surgical management are given in Table 1. One hundred
168 and forty-seven patients had undergone non-conservative surgery (bilateral salpingo-

169 oophorectomy +/- hysterectomy). Sixty-five patients had undergone conservative surgery: 14
170 had a unilateral salpingo-oophorectomy, 39 had a unilateral salpingo-oophorectomy with
171 contralateral cystectomy and 12 had a cystectomy. The ovarian tumor had been initially managed
172 laparoscopically in 73 patients. A macroscopic residual tumor had been observed in 61 cases (\geq
173 2 cm in 11).

174 The histologic results are detailed in Table 1. Among the 212 patients, 50 had stage-II
175 disease and 162 stage-III. Bilateral tumors were observed in 149 patients. One hundred and
176 seventy patients had noninvasive implants and 33 invasive implants. Nine patients had
177 undetermined implants, because the samples were too small to accurately evaluate the underlying
178 status. One hundred and twenty-five (59%) patients had peritoneal implants at least at 3 different
179 peritoneal sites. The locations of peritoneal sites are detailed in Table 1. The most frequent site
180 of peritoneal spread was omentum (Table 1). Sixty-five patients received adjuvant therapy: 52
181 adjuvant chemotherapy, 5 external radiation therapy and 8 both treatments.

182 Table 2 compares characteristics of patients according to the types of implants. Lymph
183 node resection, stage-III disease, stromal microinvasion (microinvasive carcinoma), number of
184 peritoneal sites involved ≥ 3 and the use of adjuvant treatment were statistically more frequent in
185 patients having invasive implants (extraovarian LGSC)(Table 2).

186 The median duration of follow-up was 115 months (range, 12-512). Follow-up was ≥ 5
187 and 10 years respectively in 125 (62%) and 80 (38%) patients.

188 Seventy recurrences were observed in a delay from 4 to 271 months after the first surgery,
189 28 of them (40%) recurring in the form of invasive disease. Twenty-one (30%) recurrences were
190 observed after 5 years. Site(s) of recurrences (some patients had multiple sites) were: the
191 remaining ovary after conservative surgery in 33; pelvic cavity in 16; abdomino-pelvic
192 peritoneum in 26; nodes in 12; bowel in 6; and other sites in 3 (vagina in 1 and chest in 2).

193 In 28 patients, recurrence was classified as “invasive disease”: 5 cases in the form of
194 invasive peritoneal implants (extraovarian LGSC), 17 in the form of LGSC and 4 in the form of
195 psammocarcinoma (subtype of invasive relapse was unknown in two patients). Eighteen patients
196 died, 12 from the ovarian disease, in a median delay of 21 to 315 months after the initial surgery.
197 Prognostic factors of recurrences in the form of invasive disease are detailed in Table 3. Non-
198 conservative surgery (HR=7[2.35-20.87], p=.0002), invasive implants (HR=5.37[1.29-22.26],
199 p=.013), and 3 or more peritoneal sites (HR=3.56 [1.11-11.39], p=.024) were identified as
200 predictors of recurrence in the form of invasive disease (Table 3).

201 OS at 5 and 10 years was 99% and 97% respectively. DFS at 5 and 10 years was 73% and
202 62% respectively. Prognostic factors on OS and DFS in univariate and multivariate analyses are
203 studied in Tables 4 and 5. Univariate analysis identified 2 unfavorable prognostic factors on
204 DFS: the use of a conservative treatment (HR=5.5[3.33-9.08], p<.0001) and the presence of 3 or
205 more peritoneal sites with implants (HR=1.65[1.01-2.72], p=.045). The use of adjuvant
206 treatment is a favourable prognostic factor on DFS (HR=0.53[0.31-0.89], p=.014). On OS, 2
207 unfavorable prognostic factors were identified: the presence of 3 or more peritoneal sites with
208 implants (HR=3.02[0.96-9.53], p=.049), and the presence of stromal microinvasion
209 (microinvasive carcinoma)(HR=3.19[1.12-9.1], p=.022)(Table 4). OS and DFS, according to the
210 type of surgical treatment (conservative or non-conservative) and the number of peritoneal sites
211 with implants (< or ≥ 3), are shown in Figures 1 and 2. Invasive implants were not associated
212 with DFS (HR=1.39[0.77-2.51], p=.27), nor OS (HR=1.76[0.57-5.47], p=.32)(Figure 1).

213 The multivariate analysis identified 2 independent unfavorable factors on DFS: the use of
214 conservative surgery and the presence of 3 or more peritoneal sites with implants (Table 5). The
215 single unfavorable independent prognostic factor on OS was the presence of stromal
216 microinvasion (microinvasive carcinoma)(Table 5).

217

218 *Discussion*

219 The prognosis and management of advanced-stage APSTs continue to be debated. Only 8
220 studies reported an appreciable number of cases (> 50 patients/Table
221 6)[4,5,8,14,16,18,19,20,21,24]. Furthermore, as death is a rare event in this disease, very few
222 series reported an analysis of prognostic factors on OS, the latter being, as a matter of fact, the
223 sole criterion that allows a real analysis of the impact of different factors on the survival itself
224 [22]. Some authors used the recurrence rates, others the rate of progression (or relapse in the
225 form of carcinoma (or invasive implants), when few series only analyzed the impact of survival,
226 particularly OS (Table 6)[4,5,8,14,16,18,19,20,21,23,24]. This is one of the strengths of this
227 series. As we included the largest series of stage-II/III APSTs reported, analysis on DFS, as well
228 as OS, is now possible and therefore valuable.

229 Looking at the first analysis that we have done about the risk of recurrence in the form of
230 invasive disease, 3 impact factors were identified: the type of surgery (conservative or non-
231 conservative), the number of peritoneal sites with implants, and the type of implants. Focusing
232 on the type of surgery, the use of a conservative treatment seems to decrease the risk of
233 recurrence in the form of carcinoma or invasive disease. We know that the use of a conservative
234 treatment increases the rate of relapse in APSTs, but without any deleterious impact on the
235 survival (because most recurrences are new borderline disease tumors with an excellent
236 prognosis, or relapse in the form of noninvasive implants)[6]. These points explain the OS and
237 DFS observed, according to both types of surgical treatment in this series. Furthermore,
238 conservative surgery was proposed in such a context, in a highly selected group of patients with
239 less extensive disease, and/or mostly in patients with noninvasive implants (implants)[25]. This
240 explains the strong correlation that we observed with a reduced risk of invasive recurrence in

241 patients undergoing fertility sparing surgery. Nevertheless, this result is not a statistical
242 demonstration of the protective effect of the conservative treatment, but potentially an artificial
243 result related to the selection of a subgroup with less aggressive disease.

244 The second factor that we identified, impacting the risk of invasive recurrence analysis is
245 the number of peritoneal sites with implants (Tables 2-4; Figure 2). This is a major finding, since
246 it is the sole prognostic factors identified in this series that impact at the same time the risk of
247 relapse in the form of carcinoma, the DFS and the OS (in the univariate analysis). But there are 2
248 potential weaknesses in this result, because the use of a factor based on $<$ or ≥ 3 peritoneal sites
249 with implants could be highly questioned. The first weakness is related to the potential link
250 between the number of implants and the surgical procedures used to staged and remove
251 peritoneal spread varying from surgeon to surgeon. On the other hand, a large majority of
252 patients had multiple peritoneal biopsies and omentectomy (Table 1). Furthermore, more than
253 2/3 of patients had complete macroscopic resection of their peritoneal spread and 23% had small
254 sized macroscopic residual disease in the form of small lesion on small bowel (Table 1). These 2
255 factors imply that the number of peritoneal sites with disease is probably not strongly linked with
256 the type of surgical procedures used. The second weakness about this prognostic factor is one of
257 real concern and is related to the most “accurate” tool to measure the “spread” of the disease in
258 the peritoneal cavity. The most universal tool to measure it is the Peritoneal Cancer Index, which
259 defines 13 abdominal regions and scores the peritoneal spread from 0 to 3 [26]. This tool has
260 been widely validated in primary peritoneal surface malignancy or peritoneal carcinomatosis for
261 gastro-intestinal tract, but its reliability remains discussed in ovarian cancer.²⁷ In borderline
262 ovarian disease, where the peritoneal spread has really a different prognosis than in carcinoma,
263 the best tool to measure the degree of tumoral burden in the peritoneal surfaces is not clearly
264 determined remains absolutely unclear. Not one paper focused on this question. This is why we

265 used a factor previously used in other analyses defined as the number of histological proven sites
266 with implants with a cut-off at 3 [13,15]. This measure is reliable and reproducible even if,
267 potentially, highly debatable. Clearly, however, our results suggest there is a need to define and
268 use an adequate and accurate tool to measure the degree of peritoneal spread in APSTs. Anyway,
269 the meaning of this result is that patients with a more important peritoneal spread had a higher
270 rate of recurrence in the form of carcinoma and a deleterious impact on DFS and OS (in the
271 univariate analysis).

272 The current management (surgery) is not different in patients having $<$ or \geq 3 peritoneal
273 sites involved. But this major result raised several therapeutic issues that need to be evaluated in
274 further studies: is fertility sparing surgery oncologically safe, and so, allowed for patients with \geq
275 peritoneal 3 sites involved?; does a second-look surgery have to be discussed in this subgroup?
276 At least, whereas the optimal way to follow patients with stage-II/III APSTs after the debulking
277 surgery remains discussed [28], this finding raises also the important issues that need to be
278 solved about the best way to follow patients having \geq 3 sites involved (clinical examination, but
279 combined with blood markers, and routine abdomino-pelvic imaging; if so, which kind, and at
280 which frequency?). In the multivariate analysis, the stromal microinvasion (microinvasive
281 carcinoma) is a prognostic impact on OS (Table 4). This point could be explained by the fact that
282 such tumors (stage-II/III APSTs with stromal microinvasion/microinvasive carcinoma) are very
283 close to “authentic” LGSC [9,29]. So, the limit between both entities is really thin and depends
284 both on the skill of the pathologist and the quality of the sampling on initial specimen.

285 The second major result of our series is the fact that including more patients and
286 extending the follow-up duration (which is now at nearly 10 years in terms of median), leads to
287 the disappearing of the subtype of implants as a prognostic factor of OS. This means that the
288 lethality impact is not statistically different in noninvasive implants (implants) and invasive

289 implants (extraovarian LGSC)(Figure 1). Previous studies debated the role of histologic
290 subtypes of peritoneal implants (invasive or non-invasive ones) as a prognostic factor.^{4,6} In the
291 series published by Longacre *et al.* 15 years ago, involving 113 patients with a stage-II-IV serous
292 LMPOT (with follow-up > 5 year), the only prognostic factor identified in the multivariate
293 analysis was the type of peritoneal implant [4]. But on the other hand, the initial experience from
294 the MD Anderson published by Gershenson *et al.* nearly 20 years ago is also of great interest
295 [18,19]. As a matter of fact, he reported a large series of patients with serous borderline disease
296 and peritoneal implants. It consisted of a series of 73 patients with non-invasive implants and 39
297 with invasive implants [18,19]. The rate of patients who developed progressive or recurrent
298 tumor was 30% [18,19]. It is interesting to note that in these series, the rate of recurrence
299 observed in patients with invasive and non-invasive peritoneal implants was similar [18,19].
300 Most of them recurred with evolutive invasive disease. In the 73 patients with non-invasive
301 disease, 22 relapsed [18,19]. In 20 of them, histologic analysis of the recurrence was possible. In
302 6 patients, a borderline recurrent tumor was observed. In 14 patients (20%), invasive serous
303 carcinoma was observed [18,19]. More recently, the major ROBOT trial, involving 950 patients
304 with a borderline ovarian tumor (155 patients having APSTs with implants: noninvasive in 132
305 and invasive in 23), showed similar results [24]. The specific numbers of recurrences in both
306 groups of implants are not detailed, but the subtypes of implants had no impact on progression-
307 free survival [24]. Finally, the results we reported here have a similar interpretation to both the
308 initial experience of Gershenson *et al.* and the recent ROBOT trial study.

309 One explanation for such differences between results reported on the potential prognostic
310 impact of the type of implant could be related to the duration of follow-up. Interestingly, in 2006
311 Silva *et al.* published an important paper on a series of 80 patients with noninvasive implants
312 with a minimum follow-up > 5 years [30]. The time to recurrence was analyzed: only 8/35

313 patients relapsed within 5 years after treatment of their ovarian tumor [30]. This could explain
314 why the type of implants “disappeared” as a prognostic factor in the present series, compared to
315 our initial analysis. As suggested by this series reported by Silva *et al.* and our results (Figure 1
316 on OS), invasive recurrence (and subsequent deaths due to the disease) observed in invasive
317 implants (extraovarian LGSC) happened earlier, and invasive relapse observed in patients with
318 noninvasive implants (implants) occurred later, and then could not be screened if the follow-up
319 duration was too short. By extending the follow-up, particularly in patients with a potentially
320 “long” history of their disease (noninvasive implants), the prognostic significance of the type of
321 implants disappeared. In the current series, 30% of recurrences were observed after 5 years
322 following the surgical treatment of their initial disease. These results underline then the need of a
323 very long follow-up in APSTs with peritoneal spread, whatever the type of implants.

324 In the same current series, after a long-term follow-up, type of peritoneal implants is no
325 longer a prognostic factor on OS. Implants ≥ 3 peritoneal sites seem to impact significantly the
326 risk of recurrence in the form of invasive disease and DFS and OS (in univariate analysis). These
327 results suggest that this subgroup of patients would be considered as a “high risk” group, needing
328 then to explore specific unanswered questions about it (accurate peritoneal spread evaluation,
329 safety of conservative surgery, specific modalities of follow-up...). The other major point of the
330 study is the need for a very long follow-up > 10 years in patients with APSTs and implants.

331

332 *The authors have no conflict of interest related to this study.*

333

334

335 Author contribution

336

337 Study conception and design:

338 Morice P

339 Gouy S

340
341 Acquisition of data:
342 Maria S
343 Faron M
344
345 Analysis and interpretation of data:
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354 Drafting of manuscript:
355 All authors
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References

- 357
358
- 359 1. Taylor HC. Malignant and semi-malignant tumors of the ovary. *Surg Gynecol Obstet.*
360 1929; 48: 204-230.
- 361
- 362 2. Kanat-Pektas M, Ozat M, Gungor T, Dikici T, Yilmaz B, Mollamahmutoglu L. Fertility
363 outcome after conservative surgery for borderline ovarian tumors: a single center experience.
364 *Arch Gynecol Obstet.* 2011; 284: 1253–1258
- 365
- 366 3. Deavers MT, Gershenson DM, Tortolero-Luna G et al. Micropapillary and cribriform
367 patterns in ovarian serous tumors of low malignant potential. A study of 99 advanced-stage
368 cases. *Am J Surg Pathol.* 2002; 26: 1129-1141.
- 369
- 370 4. Longacre TA, McKenney JK, Tazelaar HD, Kempson RL, Hendrickson MR. Ovarian
371 serous tumors of low malignant potential (borderline tumors). Outcome-based study of 276
372 patients with long-term (> 5-year) follow up. *Am J Surg Pathol.* 2005; 29: 707-723.
- 373
- 374 5. Seidman JD, Kurman RJ. Subclassification of serous borderline tumors of the ovary into
375 benign and malignant types. A clinicopathologic study of 65 advanced stage cases. *Am J Surg*
376 *Pathol.* 1996; 20: 1331-1345.
- 377
- 378 6. Morice P, Uzan C, Fauvet R, Gouy S, Duvillard P, Darai E. Borderline ovarian tumour:
379 pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. *Lancet Oncol.*
380 2012; 13 :e103-115.
- 381

- 382 7. Bell DA, Scully RE. Serous borderline tumors of the peritoneum. *Am J Surg Pathol.*
383 1990; 14: 230-239.
- 384
- 385 8. Bell DA, Weinstock MA, Scully RE Peritoneal implants of ovarian serous borderline
386 tumors. Histologic features and prognosis. *Cancer* 1988; 62: 2212-2222.
- 387
- 388 9. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of tumours
389 of female reproductive organs. 4th Edition. IARC. Lyon, 2014.
- 390
- 391 10. Lackman F, Carey MS, Kirk ME et al. Surgery as sole treatment for serous borderline
392 tumors of the ovary with noninvasive implants. *Gynecol Oncol.* 2003; 90: 407-412.
- 393
- 394 11. Colombo N, Sessa C, Bois A du, Ledermann J, McCluggage WG, McNeish I, et al.
395 ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and
396 molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann*
397 *Oncol.* 2019; 30: 672-705.
- 398
- 399 12. Leary A, Petrella MC, Pautier P et al. Adjuvant platinum-based chemotherapy for
400 borderline serous ovarian tumors with invasive implants. *Gynecol Oncol.* 2014; 132: 23-27.
- 401
- 402 13. Morice P, Camatte S, Rey A et al. Prognostic factors for patients with advanced stage
403 serous borderline tumours of the ovary. *Ann Oncol.* 2003; 14: 592-598.
- 404

- 405 14. Zanetta G, Rota S, Chiari S et al. Behavior of borderlin tumors with particular interest to
406 persistence, recurrence, and progression to invasive carcinoma : A prospective study. *J Clin*
407 *Oncol.* 2001; 19: 2656-2664.
- 408
- 409 15. Kane A, Uzan C, Rey A, Gouy S, Camatte S, Pautier P, et al. Prognostic factors in
410 patients with ovarian serous low malignant potential (borderline) tumors with peritoneal
411 implants. *Oncologist* 2009; 14: 591-600.
- 412
- 413 16. Shih KK, Zhou QC, Aghajanian C et al. Patterns of recurrence and role of adjuvant
414 chemotherapy in stage II-IV serous ovarian borderline tumors. *Gynecol Oncol.* 2010; 119: 270-
415 273.
- 416
- 417 17. Prat J; FIGO Committee on Gynecologic Oncology.. Staging classification for cancer of
418 the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet.* 2014 ;124: 1-5.
- 419
- 420 18. Gershenson D, Silva EL, Tortolero-Luna G et al. Serous Borderline Tumors of the Ovary
421 with Non invasive Peritoneal Implants. *Cancer* 1998; 83: 2157-263.
- 422
- 423 19. Gershenson D, Silva E, Levy L et al. Ovarian Serous Borderline Tumors with Invasive
424 Peritoneal Implants. *Cancer* 1998; 82: 1096-1103.
- 425
- 426
- 427

- 428 20. Vang R, Hannibal CG, Junge J, Frederiksen K, Kjaer SK, Kurman RJ. Long-term
429 Behavior of Serous Borderline Tumors Subdivided Into Atypical Proliferative Tumors and
430 Noninvasive Low-grade Carcinomas: A Population-based Clinicopathologic Study of 942 Cases.
431 *Am J Surg Pathol.* 2017; 41: 725-737.
432
- 433 21. Hannibal CG, Vang R, Junge J, Frederiksen K, Kurman RJ, Kjaer SK. A nationwide
434 study of ovarian serous borderline tumors in Denmark 1978-2002. Risk of recurrence, and
435 development of ovarian serous carcinoma. *Gynecol Oncol.* 2017; 144 :174-180.
436
- 437 22. Trimble CL, Kosary C, Trimble EL. Long-term survival and patterns of care in women
438 with ovarian tumors of low malignant potential. *Gynecol Oncol.* 2002; 86: 34-37.
439
- 440 23. Prat J, de Nictolis M. Serous borderline tumors of the ovary. A long-term follow-up study
441 of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. *Am J Surg*
442 *Pathol.* 2002; 26; 1111-1128.
443
- 444 24. du Bois A, Ewald-Riegler N, de Gregorio N et al. Borderline tumours of the ovary: A
445 cohort study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group. *Eur J*
446 *Cancer.* 2013; 49: 1905-1914.
447
- 448 25. Uzan C, Kane A, Rey A, Gouy S, Duvillard P, Morice P. Outcomes after conservative
449 treatment of advanced-stage serous borderline tumors of the ovary. *Ann Oncol.* 2010; 21: 55-60.
450

- 451 26. Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention
452 and treatment of peritoneal carcinomatosis and sarcomatosis. *Sem Surg Oncol.* 1998; 14: 254-
453 261
454
- 455 27. Gasimli K, Braicu EI, Richter R, Chekerov R, Sehouli J. Prognostic and Predictive Value
456 of the Peritoneal Cancer Index in Primary Advanced Epithelial Ovarian Cancer Patients After
457 Complete Cytoreductive Surgery: Study of Tumor Bank Ovarian Cancer. *Ann Surg Oncol.* 2015;
458 22: 2729-2937.
459
- 460 28. Uzan C, Kane A, Rey A, Gouy S, Pautier P, Lhomme C, et al. How to follow up
461 advanced-stage borderline tumours? Mode of diagnosis of recurrence in a large series stage II-III
462 serous borderline tumours of the ovary. *Ann Oncol.* 2011; 22: 631-635.
463
- 464 29. Hauptmann S, Friedrich K, Redline R, Avril S. Ovarian borderline tumors in the 2014
465 WHO classification: evolving concepts and diagnostic criteria. *Virchows Arch Int J Pathol.*
466 2017;470(2):12542.
467
- 468 30. Silva EG, Gershenson DM, Malpica A, Deavers M. The recurrence and the overall
469 survival rates of ovarian serous borderline neoplasms with noninvasive implants is time
470 dependent. *Am J Surg Pathol.* 2006; 30: 1367-1371.
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475 **Table 1.** Characteristics of 212 patients.

	n	%
Surgical procedures		
Non-conservative	147	(69%)
Conservative	65	(31%)
Omentectomy	178	(84%)
Peritoneal biopsies	170	(80%)
Pelvic/para-aortic lymphadenectomy	59	(27%)
Residual tumour		
No	150	(71%)
Yes	61	(28%)
< 2 cm	50	(23%)
> 2 cm	11	(5%)
Micropapillary pattern*		
No	106	(50%)
Yes	92	(43%)
Unknown	14	(7%)
Stromal microinvasion**		
No	106	(50%)
Yes	96	(45%)
Unknown	10	(5%)
Peritoneal Implants		
Noninvasive***	170	(52%)
Invasive****	33	(16%)
Not determined	9	(4%)
Lymph node status		
Negative node	38	(18%)
Positive node	21	(10%)
Location of implants		
Ovarian surface (autoimplants)	126	(59%)
Omentum	130	(61%)
Douglas pouch	74	(35%)
Uterine serosa	71	(33%)
Tubes	63	(30%)
Periton. between bladder and uterus	64	(30%)
Peritoneum Douglas pouch	74	(35%)
Pelvic peritoneum (lateral)	62	(30%)
Periton. utero-sacral ligaments	11	(5%)
Parametria	9	(4%)
Glisson capsula	6	(3%)
Para-colic gutters	45	(21%)
Bowel (small & large)	41	(19%)
Rectum serosa	24	(11%)
Appendix	10	(3%)

*: Noninvasive low grade serous carcinoma, according to the WHO 2014 classification.

**Microinvasive carcinoma, according to the WHO 2014 classification.

***: Implants, according to the WHO 2014 classification.

****: Extraovarian low grade carcinoma, according to the WHO 2014 classification.

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477 **Table 2.** Characteristics of patients according to the subtypes of implants.

Variable	Type	Noninvasive implants*	Invasive implants**	p	Total (n=212)
Non-conservative surgery	No	56 (32,9%)	8 (24,2%)	.33	65 (30,7%)
	Yes	114 (67,1%)	25 (75,8%)		147 (69,3%)
Conservative treatment	No	114 (67,1%)	25 (75,8%)	.33	147 (69,3%)
	Yes	56 (32,9%)	8 (24,2%)		65 (30,7%)
Lymph node resection	No	129 (75,9%)	17 (51,5%)	.0044	153 (72,2%)
	Yes	41 (24,1%)	16 (48,5%)		59 (27,8%)
Residual tumor	No	124 (72,9%)	25 (75,8%)	.74	151 (71,2%)
	Yes	46 (27,1%)	8 (24,2%)		61 (28,8%)
Stage	II	43 (25,3%)	3 (9,1%)	.042	50 (23,6%)
	III	127 (74,7%)	30 (90,9%)		162 (76,4%)
Micro-papillary patterns***	No	90 (54,9%)	14 (45,2%)	.32	106 (53,5%)
	Yes	74 (45,1%)	17 (54,8%)		92 (46,5%)
Stromal micro-invasion****	No	93 (56%)	10 (31,2%)	.01	106 (52,5%)
	Yes	73 (44%)	22 (68,8%)		96 (47,5%)
Number peritoneal site \geq 3	No	73 (43,2%)	7 (21,2%)	.018	86 (40,8%)
	Yes	96 (56,8%)	26 (78,8%)		125 (59,2%)
Adjuvant treatment	No	139 (81,8%)	7 (21,2%)	<.0001	146 (68,9%)
	Yes	31 (18,2%)	26 (78,8%)		66 (31,1%)

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*: Implants according to the WHO 2014 classification; **: Extra-ovarian low grade carcinoma according to the WHO 2014 classification *** : Noninvasive low grade serous carcinoma according to the WHO 2014 classification; ****: Microinvasive carcinoma, according to the WHO 2014 classification.

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483**Table 3.** Prognostic factors for recurrence under the form of invasive disease.

Variable	Type	Odd Ratio	p value
Cystectomy	No	1	.09
	Yes	0,2 [0,02-1,74]	
Lymph node resection	No	1	.2
	Yes	2,1 [0,67-6,57]	
Non-conservative surgery	No	1	.0002
	Yes	7 [2,35-20,87]	
Conservative treatment	No	1	.0002
	Yes	0,14 [0,05-0,43]	
Stage	II	1	.49
	III	1,49 [0,48-4,68]	
Stromal microinvasion*	No	1	.61
	Yes	1,29 [0,48-3,47]	
Micropapillary patterns**	No	1	.13
	Yes	2,16 [0,79-5,92]	
Residual disease	No	1	.52
	Yes	1,4 [0,5-3,89]	
Noninvasive implants***	No	1	.013
	Yes	0,19 [0,04-0,77]	
Invasive implants****	No	1	.013
	Yes	5,37 [1,29-22,26]	
Number peritoneal sites ≥ 3	No	1	.024
	Yes	3,56 [1,11-11,39]	
Nodal involvement	No	1	.0072
	Yes	67362619,57 [0-Inf]	
Adjuvant treatment	No	1	.29
	Yes	1,79 [0,61-5,25]	

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*: Microinvasive carcinoma, according to the WHO 2014 classification.

**: Noninvasive low grade serous carcinoma, according to the WHO 2014 classification.

***: Implants, according to the WHO 2014 classification.

****: Extraovarian low grade carcinoma, according to the WHO 2014 classification.

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493**Table 4.** Prognostic factors on Overall Survival (OS) and Disease Free Survival/DFS (univariate analysis).

Variable	Type	OS (HR) IC 95%	p value	DFS (HR) IC 95%	p value
Lymph node resection	No	1	.91	1	.28
	Yes	0,94 [0,33-2,68]		0,72 [0,41-1,25]	
Non-conservative surgery	No	1	.93	1	<.0001
	Yes	1,06 [0,29-3,86]		0,18 [0,11-0,3]	
Conservative treatment	No	1	.93	1	<.0001
	Yes	0,94 [0,26-3,41]		5,5 [3,33-9,08]	
FIGO Stage	II	1	.35	1	.85
	III	1,71 [0,55-5,38]		1,05 [0,62-1,8]	
Stromal microinvasion*	No	1	.022	1	.065
	Yes	3,19 [1,12-9,1]		1,56 [0,97-2,5]	
Micropapillary patterns**	No	1	.73	1	.64
	Yes	1,19 [0,44-3,23]		1,12 [0,7-1,79]	
Residual disease	No	1	.39	1	.155
	Yes	1,57 [0,56-4,41]		0,86 [0,52-1,41]	
Noninvasive implants***	No	1	.32	1	.27
	Yes	0,57 [0,18-1,76]		0,72 [0,4-1,3]	
Invasive implants****	No	1	.32	1	.27
	Yes	1,76 [0,57-5,47]		1,39 [0,77-2,51]	
Number of peritoneal sites	< 3	1	.049	1	.045
	≥ 3	3,02 [0,96-9,53]		1,65 [1,01-2,72]	
Nodal involvement	No	1	.89	1	.27
	Yes	1,11 [0,25-4,91]		0,57 [0,21-1,56]	
Positive omentum	No	1	.69	1	.4
	Yes	1,22 [0,46-3,25]		1,23 [0,76-1,98]	
Adjuvant treatment	No	1	.63	1	.014
	Yes	0,79 [0,31-2,05]		0,53 [0,31-0,89]	
Chemotherapy	No	1	.81	1	.064
	Yes	0,89 [0,35-2,29]		0,62 [0,37-1,03]	

*: Microinvasive carcinoma, according to the WHO 2014 classification.

**: Noninvasive low grade serous carcinoma, according to the WHO 2014 classification.

***: Implants, according to the WHO 2014 classification.

****: Extraovarian low grade carcinoma, according to the WHO 2014 classification.

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Table 5. Prognostic factors on Overall Survival (OS) and Disease-Free Survival/DFS (multivariate analysis).

Variable	Type	OS (HR)	p value	DFS (HR)	p value
		IC 95%		IC 95%	
Non-conservative surgery	No	1	/	1	< .0001
	Yes	/		0,18 [0,11-0,29]	
Number peritoneal sites \geq 3	No	1	.14	1	.029
	Yes	2,46 [0,68-8,86]		1,72 [1,04-2,83]	
Stromal microinvasion*	No	1	.026	1	/
	Yes	3,37 [1,06-10,7]		/	

505 *: Microinvasive carcinoma, according to the WHO 2014 classification.

Table 6. Literature review of series reporting > 50 stage II or III Atypical Proliferative Serous Tumors.

	N patients	N (%) non-invasive implants	N (%) invasive implants	Median Follow-up (months)	N recurrences		N Deaths	
					Non-invasive implants	Invasive implants	Non-invasive Implants	Invasive implants
Bell et al. ⁽⁸⁾ (1988)	56	50 (89)	6 (11)	72		NR	3	5
Seidman et al. ⁽⁵⁾ (1996)	65	52 (80)	13 (20)	99	2	7	1	6
Gerhenson et al. ^(18,19) (1998)	112	73 (65)	39 (35)	139	14	9	6	6
Zanetta et al. ⁽¹⁴⁾ (2001)*	53	28 (52)	16 (30)	70		3		0
Longacre et al. ⁽⁴⁾ (2005)**	113	85 (75)	14 (12)	60	3	4	2	5
Du Bois et al. ⁽²⁴⁾ (2013)	155	132 (85)	23 (15)	41***		NR		NR
Shih et al. ⁽¹⁶⁾ (2016)*	85	NR	36	44		14		7
Vang et al. ⁽²⁰⁾ (2017)	133	114 (86)	19 (14)	180	18	5		NR
Present series	212	170 (80)	33 (20)	115	20	8	10	4
TOTAL	829	572	176	97	57	33	22	26

*All subtypes mixed ; ** Type of implants in 3 patients who died uncertain, ; ***: Median Follow-up for the entire series; NR: Not reported

Legends of figures:

Figure 1. Overall Survival curves according to the number of peritoneal site with implants (< 3 in blue and \geq 3 in red).

Figure 2. Overall Survival curves according to the type of peritoneal implants.



