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1 **Need for risk-adapted therapy for malignant ovarian**
2 **germ cell tumors : a large multicenter analysis of**
3 **germ cell tumors' patients from French TMRG**
4 **network.**

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48

49 **Abstract**

50 **Background:** Malignant ovarian germ cell tumors are rare tumors, affecting young
51 women with a generally favorable prognosis. The French reference network for Rare
52 Malignant Gynecological Tumors (TMRG) aims to improve their management. The
53 purpose of this study is to report clinicopathological features and long-term
54 outcomes, to explore prognostic parameters and to help in considering adjuvant
55 strategy for stage I patients.

56 **Patients and Methods:** Data from patients with MOGCT registered among 13 of the
57 largest centers of the TMRG network were analyzed. We report clinicopathological
58 features, estimated 5-year event-free survival (5y-EFS) and 5-year overall survival
59 (5y-OS) of MOGCT patients.

60 **Results:** We collected data from 147 patients including 101 (68.7%) FIGO stage I
61 patients. Histology identifies 40 dysgerminomas, 52 immature teratomas, 32 yolk sac
62 tumors, 2 choriocarcinomas and 21 mixed tumors. Surgery was performed in 140
63 (95.2%) patients and 106 (72.1%) received first line chemotherapy. Twenty-two stage
64 I patients did not receive chemotherapy. Relapse occurred in 24 patients: 13 were
65 exclusively treated with upfront surgery and 11 received surgery and chemotherapy.
66 5y-EFS was 82% and 5y-OS was 92.4%. Stage I patients who underwent surgery
67 alone had an estimated 5y-EFS of 54.6% and patients receiving adjuvant
68 chemotherapy 94.4 % ($P < 0.001$). However, no impact on estimated 5y-OS was
69 observed: 96.3% versus 97.8% respectively ($P = 0.62$). FIGO stage, complete
70 primary surgery and post-operative alpha fetoprotein level significantly correlated
71 with survival.

72 **Conclusion:** Adjuvant chemotherapy does not seem to improve survival in stage I
73 patients. Active surveillance can be proposed for selected patients with a complete
74 surgical staging.

75 **Key words:** Rare Malignant Ovarian Tumors, TMRG, Prognostic Factors, Stage I

76

77 **Introduction**

78 Malignant ovarian germ cell tumors (MOGCT) are rare ovarian neoplasms,
79 accounting for 1% of all ovarian tumors. Worldwide incidence is about 0.37 per
80 100000 women/year [1]. Germ cell tumors affect mainly adolescents and young
81 women and require specific treatments different from those of malignant epithelial
82 ovarian tumors, with specific fertility sparing procedures. According to the World
83 Health Organization (WHO), MOGCT are divided into different histological subtypes :
84 dysgerminomas (accounting for 45%) and non-dysgerminomatous tumors (including
85 immature teratomas, yolk sac tumors, embryonal carcinomas, choriocarcinomas and
86 mixed germ cell tumors) [2].

87 International guidelines for treatment of women with MOGCT recommend in most
88 cases fertility-sparing surgery followed by 3-4 cycles of bleomycin, etoposide, and
89 cisplatin (BEP) adjuvant chemotherapy, even in early stages [1, 3, 4]. The current
90 treatments result in at least 90% of overall survival (OS) in women with early stage
91 MOGCT and to up to 80% of OS in patients with advanced disease [3, 5]. Almost 60-
92 70% patients with MOGCT are diagnosed at an early stage (stage I) and adjuvant
93 chemotherapy for these patients remains debatable [6]. So far, no consensus was
94 reached for these patients and more detailed paediatrics and adult's guidelines are
95 still awaited. On the one hand, recommend adjuvant chemotherapy for all MOGCT
96 reduces the risk of recurrence and results in improve EFS even for early stages. But,
97 sparing adjuvant chemotherapy in patients at increased risk of relapse may
98 subsequently correlate with an increased risk of mortality or fertility issues. On the
99 other hand, systematic adjuvant chemotherapy may result in improper overtreatment
100 and would not be appropriate. Indeed, surgery alone is often decided in young

101 women to prevent late toxicities that must be considered as a major goal in patient
102 care [1, 7, 8].

103 Randomized trials are scarce in the field of such rare tumors; the current practice is
104 derived mainly from retrospective studies and assessment from male germ cell
105 malignancies trials. Indeed, the establishment of a dedicated network to analyze
106 collected data in patients with such rare tumors is fundamental.

107 The purpose of this study was to assess the outcome of patients registered in the
108 French Rare Malignant Gynecological Tumors (TMRG) network; to identify
109 prognostic factors likely to help appropriate risk-based decisions and finally to focus
110 on stage I patients for whom the benefit of adjuvant chemotherapy and surveillance
111 following surgery was explored.

112

113 **Patients and methods**

114 **Data Collection**

115 The French network for Rare Malignant Gynecological Tumors (TMRG) established
116 in 2011 and supported by the French National Cancer Institute (INCa) has been set
117 up in order to improve management of these rare tumors with expert's opinion
118 (histological diagnosis and multidisciplinary board decision for treatment). Its
119 organization and functioning were previously described [9]. Each patient provides a
120 written informed consent, data are anonymized and registered in a national
121 database. Most of the cases are reviewed by an expert in anatomopathology and a
122 multidisciplinary board determines for each patient the best therapeutic sequence.
123 This multicenter retrospective analysis based on a prospective data collection was
124 authorized by the French data protection authority (CNIL) in June 2018. The TMRG
125 database was used to identify patients with ovarian germ cell tumor diagnosis. To
126 note, non-ovarian germ cell tumors and mature teratoma with malignant
127 transformation were excluded. Overall, 379 centers (including referent and non
128 referent centers) collected data from 7302 patients with a rare ovarian tumor. Then,
129 we carried on this case collection in the 13 largest centers among the 25 referent
130 centers of the TMRG network in France.

131

132 **Staging and tumor classification**

133 Tumors stages were defined according to the International Federation of Gynecology
134 and Obstetrics staging system for ovarian cancers (FIGO 2014) [10]. Histological
135 type was defined according to the WHO classification [11].

136 **Treatment and follow-up**

137 In the case of early-stage disease (up Ic3 FIGO), guidelines recommended salpingo
138 oophorectomy with peritoneal staging procedures (routine peritoneal cytology,
139 multiple peritoneal biopsies, and omentectomy). In the case of advanced disease, a
140 fertility-sparing approach is preferred whenever possible, especially in young women
141 which consists on unilateral salpingo oophorectomy, omentectomy, and resection of
142 macroscopic lesions on the peritoneum [3, 4]. Chemotherapy used standardized
143 international protocols for germ cells tumors: most of the patients were treated with a
144 regimen combining cisplatin and etoposide (EP), or adding bleomycin to the latter
145 regimen (BEP). While requirement of adjuvant treatment was debatable in patients at
146 early tumor stages, all patients at advanced stages received chemotherapy. Patient
147 follow-up included clinical examination, blood marker measurements (alpha
148 fetoprotein, HCG, LDH) and regular imaging closely during the first two years and at
149 gradually increasing intervals thereafter for a mean time of 5 years, according to
150 international recommendations.

151

152 **Statistics**

153 Survival rates were estimated using the Kaplan-Meier method. Overall survival was
154 calculated as the time from the date of diagnosis to the time of last follow-up or death
155 from any cause. Event-free survival (EFS) was calculated from the date of diagnosis
156 to the date of first event, defined as relapse, progressive tumor or death from any
157 cause. Univariate analysis using a log-rank test investigated potential correlations
158 between survival and patient or disease covariates. No multivariate analysis was
159 performed because of the reduced number of events in this cohort.

160

161 **Results**

162 **Patient characteristics and treatment**

163 We identified 262 patients with MOGCT in 13 referent cancer centers. Duplicates and
164 non-exclusively germ cell tumors exclusion led to finally include 147 patients
165 (Supplementary S1). Members of the pathological expert board in TMRG network
166 reviewed 112 (76.2%) tumor samples. Patient characteristics are summarized in
167 table 1. Most of patients ($N = 101$, 69%) had a stage I disease at diagnosis. The
168 median follow up was 51 [40-62] months. Survival follow up data were available for
169 137 (93.2%) patients including 94 (93%) out of the 101 patients at stage I. As
170 expected, the 3 most represented histological entities were immature teratomas,
171 dysgerminomas and yolk sac tumors (Supplementary S2). One hundred and forty
172 (95%) patients underwent primary surgery (Table 1, Supplementary S3 and S4).
173 Seventy-seven (75%) of the stage I patients had complete peritoneal staging
174 (peritoneal washings, biopsies including omentectomy) and 94 had surgery with
175 fertility preservation procedures. Sixteen patients underwent a retroperitoneal lymph
176 node evaluation and 2 were positives. Sixty-six patients were at stage IA disease, 1
177 was at stage IB and 34 were at stage IC. Intra-operative surgical spill was
178 documented in 11 cases (FIGO IC1). One hundred and six (72.1%) patients received
179 chemotherapy (Table 1, Supplementary S3 and S4). Cisplatin-based chemotherapy
180 has been administered to 106 patients and 98 patients received BEP/EP regimen.
181 Adjuvant chemotherapy was administered to 28 of the 60 stage IA-B patients and to
182 31 of the 33 stage IC patients.

183 **Outcome**

184 Estimated 5-y OS and EFS rates were 92.4% (95%CI :88%-96.8%) and 82% (95%CI
185 :75.8%-88.2%), respectively (figure 1). Twenty-four (15%) out of the 147 patients
186 relapsed including 13 patients treated with surgery alone and 11 treated with
187 adjuvant chemotherapy. All relapses occurred in the first 2 years. Overall, 8 out of the
188 147 patients died: 7 deaths occurred due to disease progression and 1 death due to
189 chemotherapy toxicity. Three patients developed a contralateral tumor (one
190 dysgerminoma, one teratoma and one yolk sac tumor). An assessment of toxicity
191 was done retrospectively. We observed febrile neutropenia (n=16), pulmonary
192 toxicities (n=10), neurotoxicities (n=8), thromboembolism events (n=7),
193 cardiovascular dysfunctions (n=2), gonadal dysfunctions (n=8) and 2 second
194 malignancies in our cohort.

195 **Early stage**

196 In the stage I patient population, the 5y-EFS rates were respectively 94.4% in
197 patients treated with adjuvant chemotherapy ($N = 59$) and 54.6% in patients who
198 underwent surgery followed by surveillance ($N = 35$) ($P < 0,00001$) (Figure 2A). The
199 5y-OS rates were similar with 96.3% and 97.8% respectively (*NS*) (Figure 2B). In the
200 17 patients who relapsed, all but 1 underwent chemotherapy. In the 35 patients
201 treated with surgery alone, 13 (37%) relapsed: 6/16 (37.5%) patients with pure
202 dysgerminoma, 3/15 (20%) immature teratoma, 3/3 (100%) YST patients and one
203 (100%) other mixed tumor. All relapsing patients were staged IA patients (Figure 3).
204 Median time to relapse was 11.5 (1-24) months. Eight of the 13 had previous
205 adequate peritoneal staging. Eleven of them received chemotherapy at relapse (1
206 refused treatment and was lost to follow-up; 1 underwent salvage surgery without
207 chemotherapy). Overall, 11/12 patients were successfully treated at relapse (one

208 missing data). The remaining patient (immature teratoma) died from septic shock
209 following grade 4 neutropenia after the first cycle of BEP chemotherapy. Among the 4
210 patients diagnosed at stage I who relapsed despite adjuvant chemotherapy, 3 had
211 received BEP as adjuvant treatment. One patient with YST died from disease
212 progression while the 3 remaining patients were alive following salvage treatment (2
213 patients received EP protocol and 1 received VeIP protocol).

214 **Advanced stage**

215 At advanced stages (FIGO II-IV), progressive disease or relapse was diagnosed in 7
216 patients (16%, Supplementary S5). Median time to relapse was 7.5 (1-15) months.
217 All patients received salvage chemotherapy : VeIP ($N = 3$), BEP ($N = 2$), Epirubicin
218 Docetaxel ($N = 1$) and Carboplatin Paclitaxel ($N = 1$). Two of them received high
219 dose chemotherapy with autologous stem-cell support. Six patients died and one was
220 salvaged with treatment (dysgerminoma, 4 BEP cycles).

221 **Prognostic factors**

222 The univariate analysis identified FIGO stage, complete surgery and post operative
223 α FP as predictive factors of OS (Table 2). No differences were found using the
224 covariates postoperative HCG, LDH level, YST subtype (trend to associate with at
225 poorer prognosis, $P = 0.076$), or presence of lymphovascular space invasion (LVSI)..

226

227

228 Discussion

229 This retrospective study is one of the largest cohort of MOGCT in adults. The major
230 finding of our study is to show, , that absence of adjuvant chemotherapy in stage I
231 MOGCT patients has no impact on estimated 5 y-OS if patients receive
232 chemotherapy at relapse. This result may help to carefully reconsider efficacy and
233 toxicity balance in stage I MOGCT.

234 Overall, survival results showed an estimated 5-year OS of 92.4% and an estimated
235 5-year EFS of 82% all tumors combined. These results are consistent with OS and
236 EFS reported in previous clinical trials [3, 11–13]

237 . Median time to relapse was 9 [1-24] months. Our series shows that relapses
238 occurred in the first 2 years following diagnosis as previously reported [15]. These
239 data highlight that active surveillance is crucial in the first 2 years. Both ESMO and
240 NCCN have released guidelines about active surveillance [1, 16]. ESMO
241 recommends clinical examination and blood markers measurements monthly for the
242 first year, 2 monthly for the second year, 3 monthly for the third year, 4 monthly for
243 the forth year and 6 monthly from the fifth to the tenth year. Moreover, patients have
244 to undergo CT chest abdomen and pelvis at 1, 3 and 12 months plus pelvic US and
245 chest X-ray regularly until 10 years. Platinum-based chemotherapy regimen using
246 BEP/EP or VIP/VeIP regimen has been offered in most patients [17, 18]. Known
247 chemotherapy-related toxicities occurred. Acute toxicities including neutropenia
248 grade ≥ 3 (70%), febrile neutropenia (7%), thrombocytopenia grade ≥ 3 (8%),
249 mucocutaneous toxicity (8%), neuropath (25-30%), ototoxicity (20-25%),
250 nephrotoxicity (3%) and pulmonary toxicity (9%) are the most common [19, 20]. Late
251 toxicities including cardiovascular disease/hypertension (6-10%), gonadal
252 dysfunction and second malignancies (relative risk ~ 1.5 – 2.1) are much less common

253 but can last a lifetime [21]. All these toxicities should be considered before
254 recommending adjuvant treatment [1]. .

255 Patients at advanced stages, all received chemotherapy. Six out of 7 relapsed
256 patients died despite salvage treatments, highlighting their poor prognosis at relapse.
257 While high dose chemotherapy with autologous stem-cell support may be proposed
258 in relapsed patients [22], the small number of patients treated did not allow any
259 conclusion. However, discussions on case-by-case basis should take place within the
260 multidisciplinary tumor board. Treatment of refractory tumors remains unsatisfactory,
261 and new approaches are needed to further improve outcomes. We believe that
262 international collaboration should be established to thoroughly analyze the biological
263 characteristics of these tumors.

264 For patients at early stages, the current questions are different and essentially
265 concern the need for therapeutic de-escalation. Indeed, preventing and minimizing
266 short-term and long-term toxicity related to chemotherapy regimen is of major
267 concern for these young patients, for whom surgery alone is likely to be curative in
268 most cases. However, international recommendations still mention the necessity of
269 adjuvant treatment consisting in 3-4 cycles of BEP chemotherapy after surgery. Our
270 study showed that 38 (37.6%) of the patients at early stage did not receive
271 chemotherapy and 13 (34%) patients relapsed. Despite a significant difference on
272 estimated 5 y-EFS, we show that absence of adjuvant chemotherapy in stage I
273 MOGCT patients has no impact on estimated 5 y-OS if patients receive
274 chemotherapy at relapse. This result is consistent with other recent studies
275 suggesting excellent survival outcome in stage I patients spared from adjuvant
276 chemotherapy [7, 20–22]

277

278 Moreover, some factors are critical to determine the risk of relapse in early stages
279 especially pathologic subtype. In this study, most patients without recurrence
280 following surgery alone who did not receive adjuvant chemotherapy were diagnosed
281 with a dysgerminoma or immature teratoma tumor, whereas all patients suffering
282 from a yolk sac tumor histology component relapsed. We believe that our data
283 confirm that systematic adjuvant chemotherapy should be applied in all stage I yolk
284 sac tumors patients as it has been already recommended [23, 26, 27]. We showed
285 that sparing stage Ia-Ib grade 1 immature teratoma and some dysgerminoma
286 patients from adjuvant chemotherapy may be a valid option following adequate
287 surgical staging, complete resection and normal post-operative serum marker levels.
288 Of note, ESGO and ESMO recently published recommendations for MOGCT
289 treatment in which surveillance is proposed for selected stage I tumors. Our series
290 shows a higher relapse rate for dysgerminomas than that observed in the Italian
291 series. This discrepancy may result from the relatively small numbers of patients in
292 both series. Therefore, as proposed for testicular seminomas with a cure rate above
293 95% [28, 29], one course of carboplatin AUC7 for dysgerminomas should be
294 investigated. Similarly, in patients with stage I non seminomatous testicular cancer,
295 1-2 adjuvant BEP cycles are appropriate to cure mainly all patients [30]. We assume
296 this treatment for non dysgerminomatous MOGCT patients should be further
297 explored. Nevertheless, this therapeutic de-escalation requires careful assessment
298 before being adopted routinely. Another important point remains the necessity of
299 optimal staging peritoneal procedures. Indeed, the omission of appropriate staging
300 peritoneal procedures seems to increase the recurrence rate, as a result of
301 underestimation of advanced stage [1]. Active surveillance should be considered in
302 confirmed stage I patients and peritoneal staging turns out to be essential to
303 guarantee adequate management.

304

305 This study presents several limitations, we performed a retrospective analysis and
306 faced with missing data especially related to pre-operative markers; due to the rarity
307 of these tumors and their general good prognosis, only univariate analysis was
308 performed. A larger international cohort with more patients and more events is
309 needed to build a valid prognostic score as proposed in patients with testicular germ
310 cell tumors [31] or as suggested by Meisel and colleagues in patients with MOGCT
311 [32].

312

313 **Conclusion**

314 Adjuvant chemotherapy should not be systematically proposed for stage I patients
315 with exception for YST. Active surveillance is an acceptable alternative. A close
316 follow-up during the first 2 years is essential. Further investigation is required to
317 determine the optimal management of patients with MOGCT at advanced stages
318 and relapsed disease. Prospective trials conducted through international
319 collaborations like the Rre Cancers Europe Initiative are needed to develop risk-
320 based treatment strategies for these rare tumors.

321

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341

342 DISCLOSURES:

343 The authors reported no conflict of interest for this article.

344

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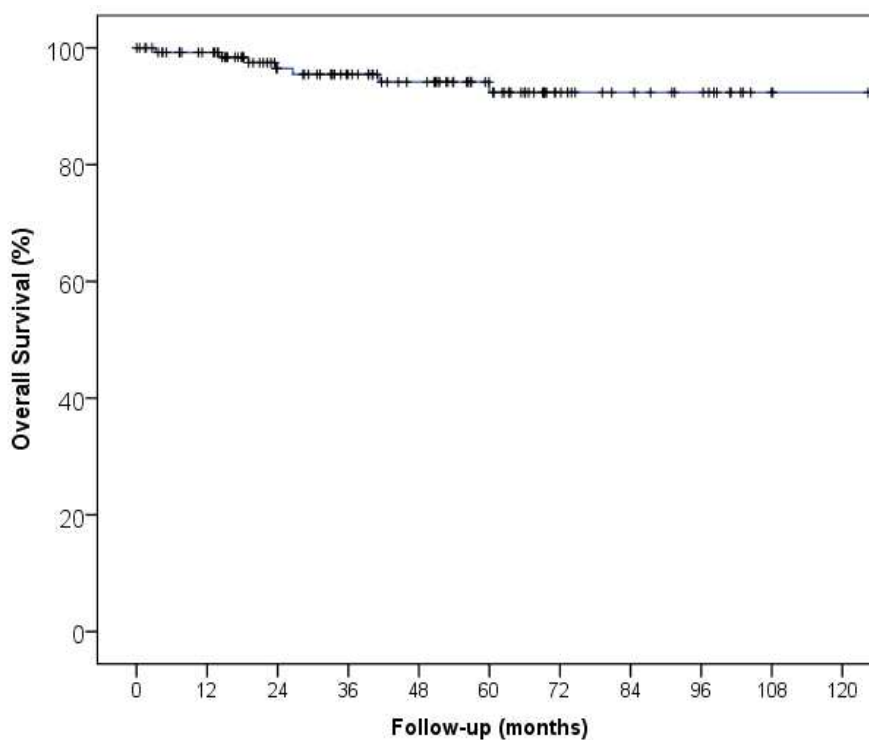
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Figure 1– Kaplan Meier Estimates of Overall Survival (A) and Event Free Survival (B)

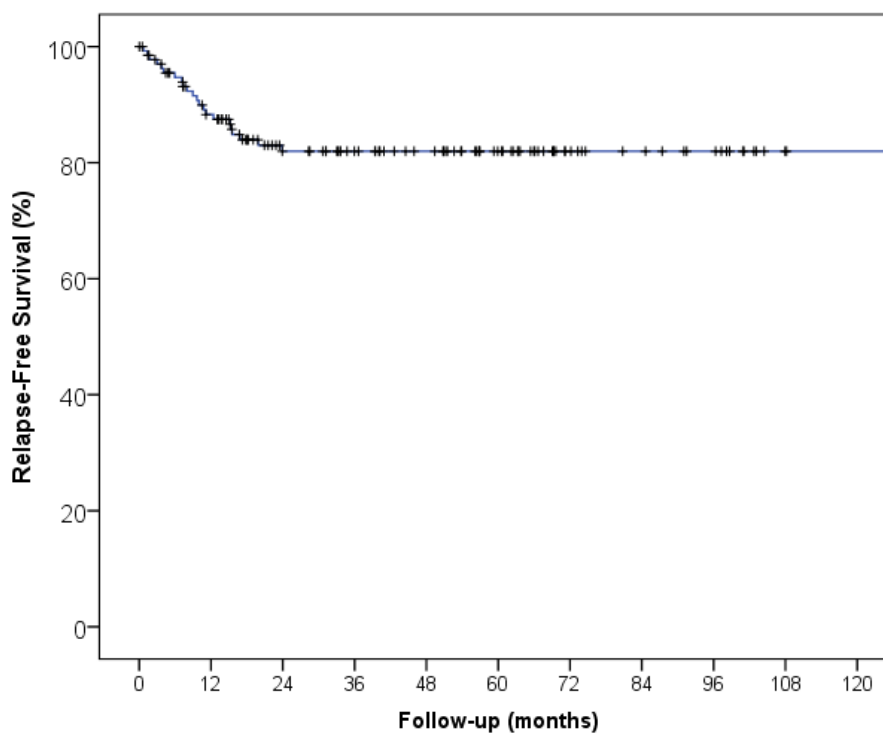
A) Overall Survival



Number of patients without event
(137 available datas)

137 122 95 81 69 51 32 26 22 12 11

B) Event Free Survival

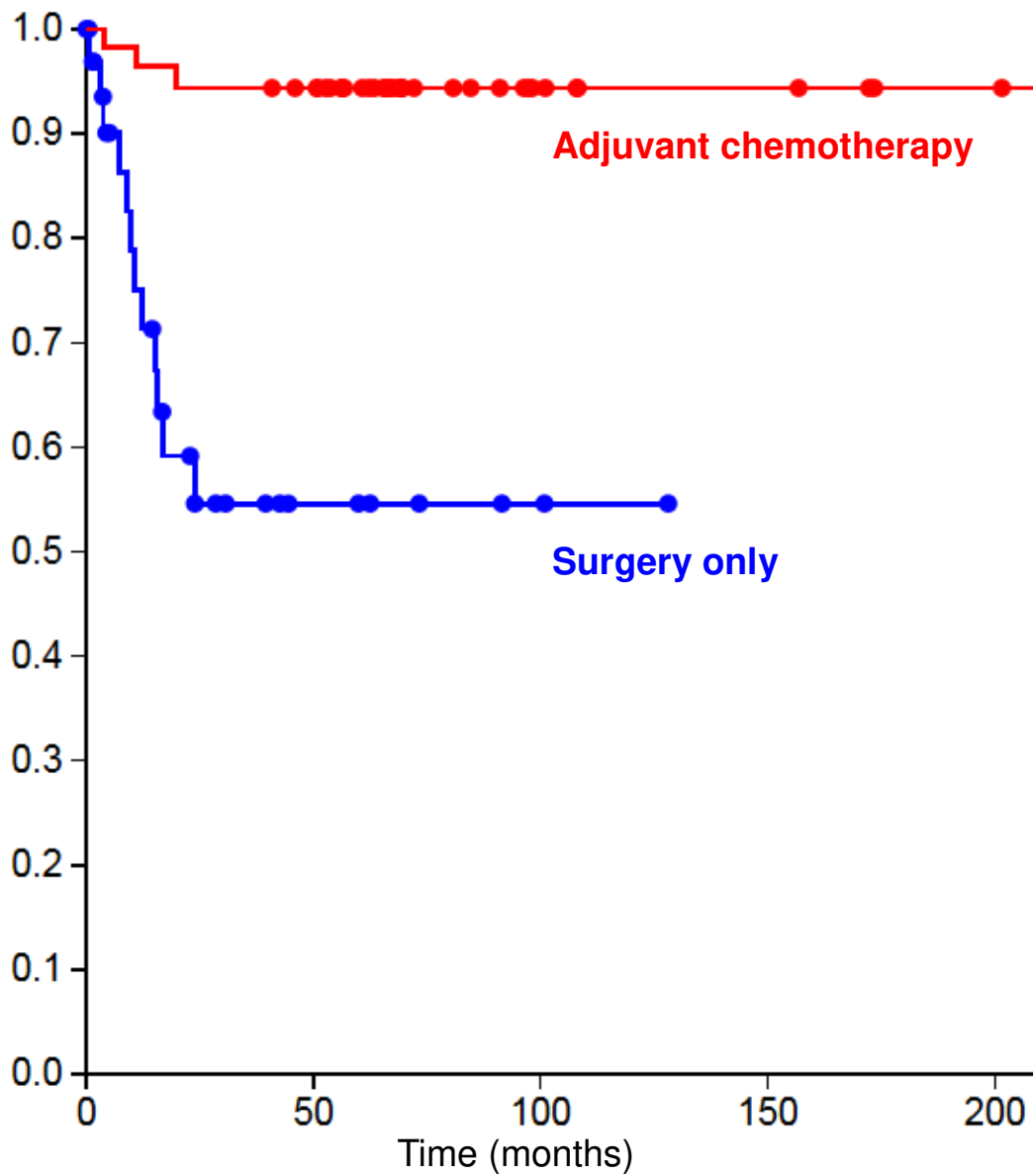


Number of patients without event
(137 available datas)

137 108 79 68 59 44 26 21 17 7 6

Figure 2– Kaplan Meier Estimates of Event Free Survival (A) and Overall Survival (B) according to adjuvant CT or surveillance following initial surgery in stage I disease

(A) Event Free Survival



(B) Overall Survival

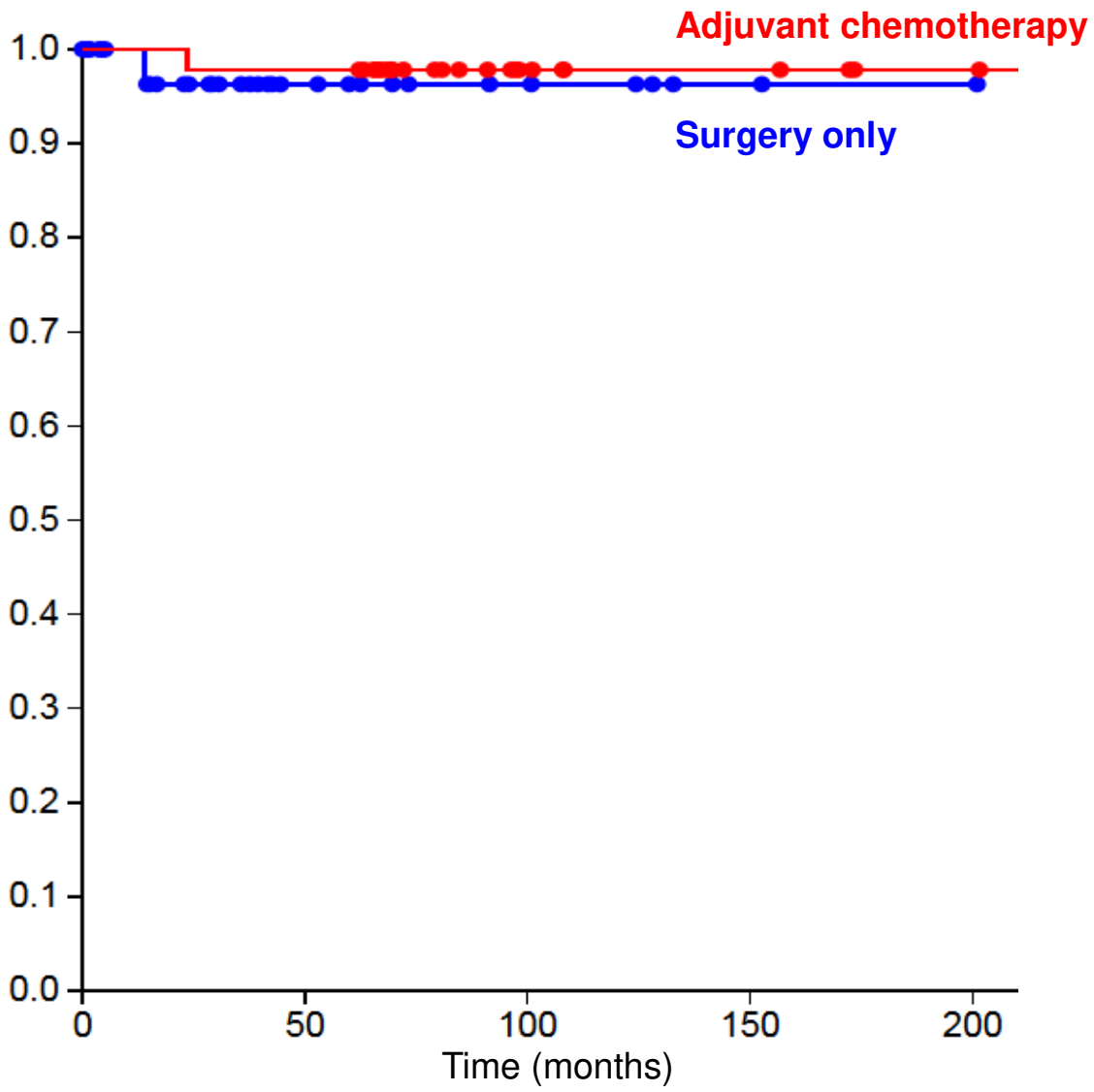
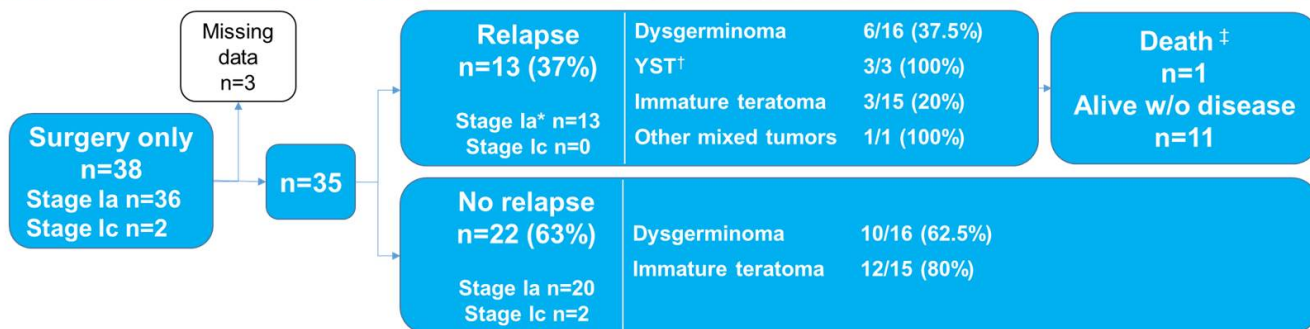


Figure 3– Outcome according to adjuvant chemotherapy or surveillance following initial surgery for stage I MOGCT

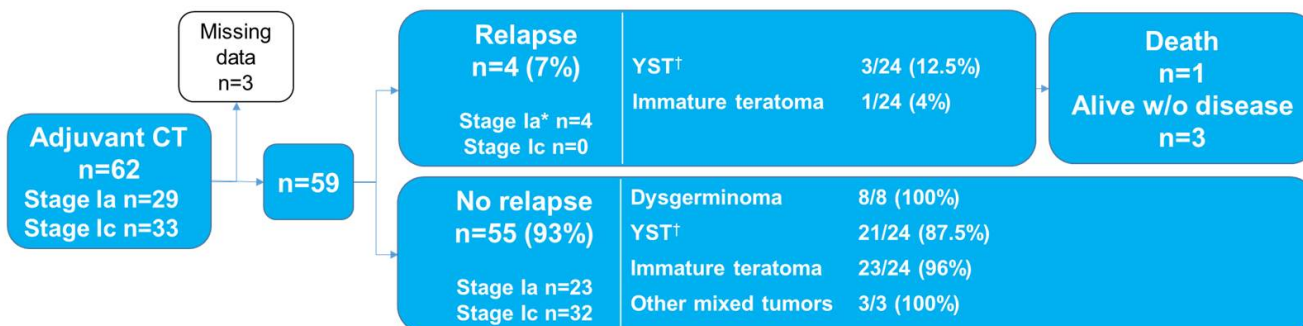
Outcome according to adjuvant chemotherapy (CT) or surveillance following initial surgery



* 8/13 patients had an adequate peritoneal staging

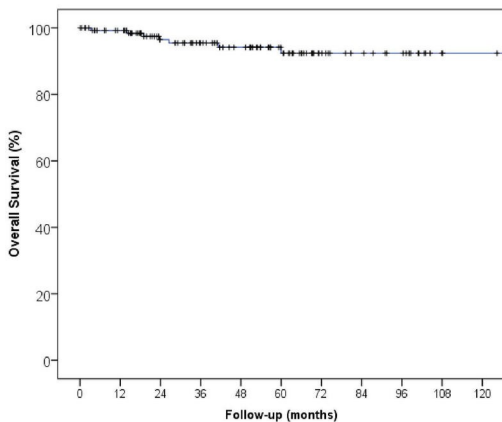
† YST category include both pure and mixed YST

‡ patient lost of follow-up (n=1), probably dead



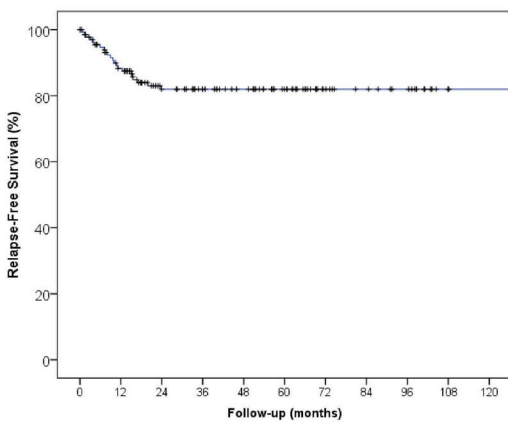
* 3/4 patients had an adequate peritoneal staging

† YST category include both pure and mixed YST



Number of patients without event
(137 available datas)

137 122 95 81 69 51 32 26 22 12 11

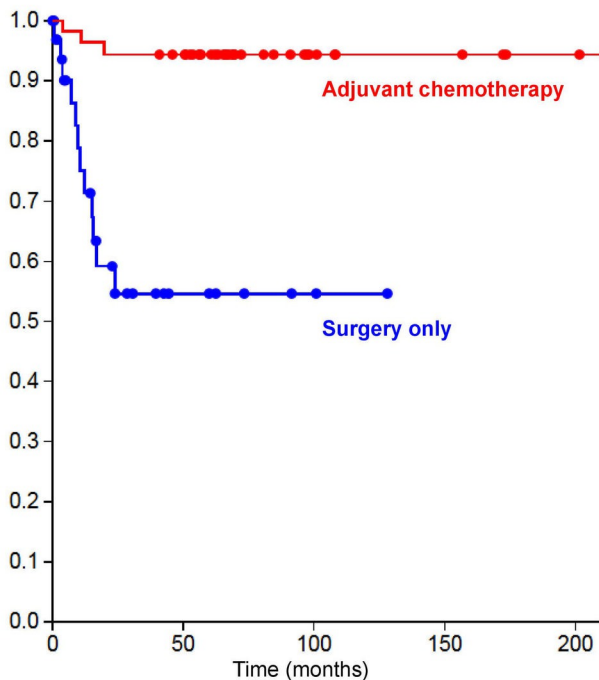


Number of patients without event
(137 available datas)

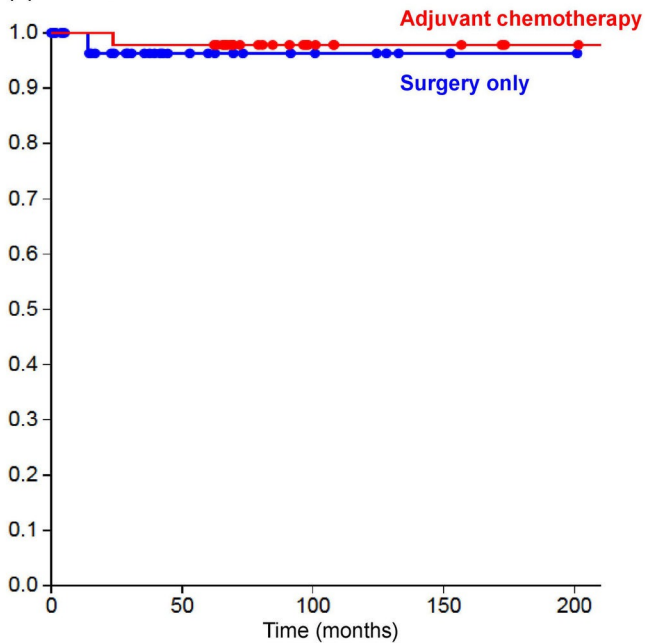
137 108 79 68 59 44 26 21 17 7 6

Figure 2– Kaplan Meier Estimates of Event Free Survival (A) and Overall Survival (B) according to adjuvant CT or surveillance following initial surgery in stage I disease

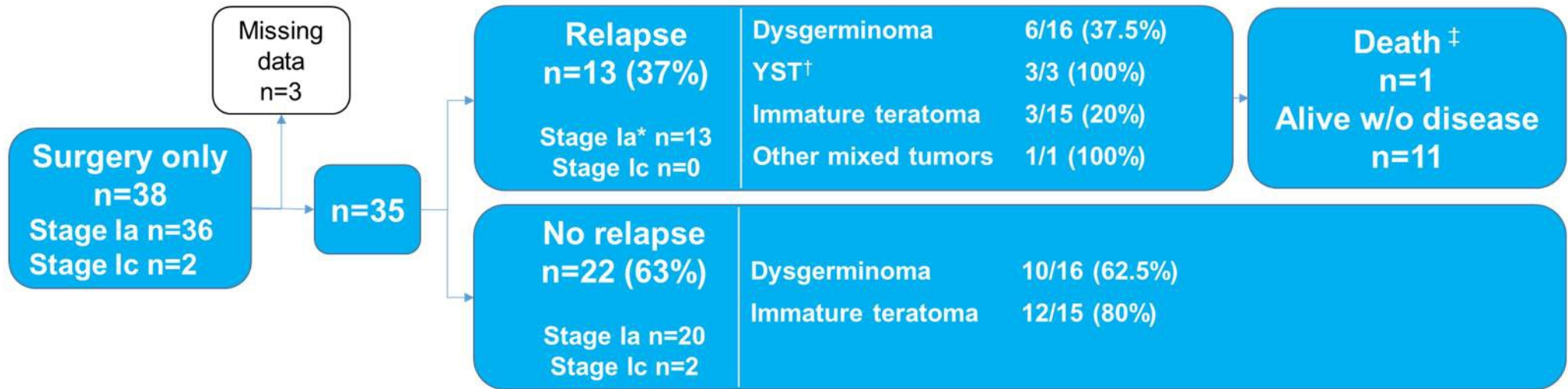
(A) Event Free Survival



(B) Overall Survival



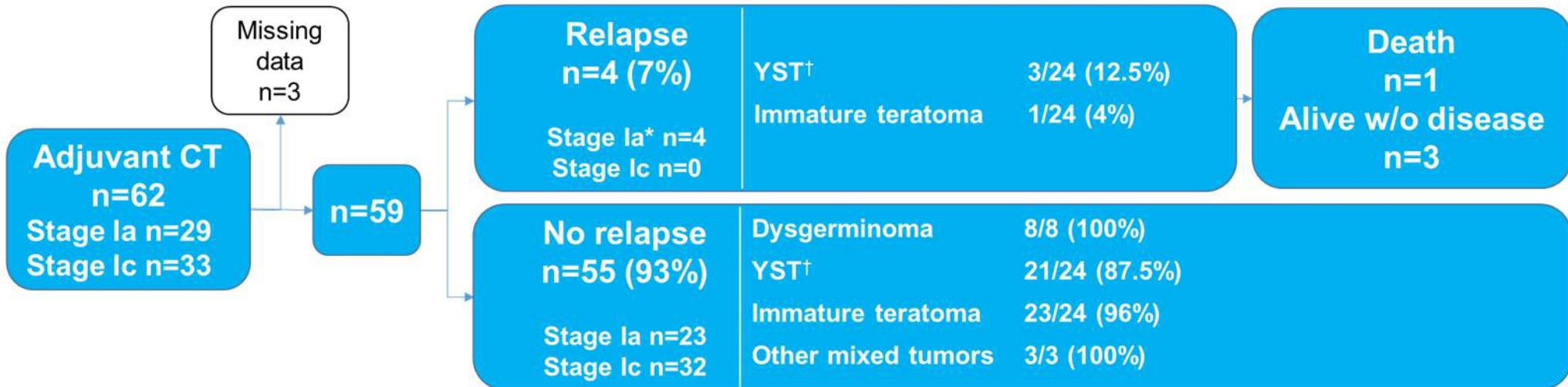
Outcome according to adjuvant chemotherapy (CT) or surveillance following initial surgery



* 8/13 patients had an adequate peritoneal staging

† YST category include both pure and mixed YST

‡ patient lost of follow-up (n=1), probably dead



* 3/4 patients had an adequate peritoneal staging

† YST category include both pure and mixed YST

Table 1 – Patient Characteristics and treatment (*N* = 147)

	N
Median age (years)	25 [15-77]
Nulligravida	81 (55.1%)
Nulliparous	88 (59.9%)
Stage at presentation	
Ia/Ib	67 (45.6%)
Ic	34 (23.1%)
II	8 (5.4%)
III	27 (18.4%)
IV	9 (6.1%)
Unknown	2 (1.4%)
Histology	
Pure MOGCT	126 (85.7%)
Dysgerminoma	40 (27.2%)
Immature Teratoma	52 (35.4%)
Yolk Sac Tumor	32 (21.8%)
Choriocarcinoma	2 (1.4%)
Mixed MOGCT	21 (14.3%)
Surgery*	
Stage I	101
Complete peritoneal staging [†] (peritoneal washings, biopsies or omentectomy)	76/101 (75%)
Fertility-sparing Surgery	94/101 (94%)
Radical Surgery	7/101 (6%)
Stage II-IV	44
Fertility-sparing Surgery	32/44 (72.7%)

Radical Surgery	12/44 (27.3%)
Chemotherapy ‡	
Stage I	100
Adjuvant chemotherapy	62/100 (62%)
No adjuvant chemotherapy	38/100 (38%)
Stage II-IV	44/44 (100%)

*missing data n=2; †missing data n=1; ‡ missing data n=3

Table 2 –Univariate analysis of 5-year OS (N = 137) *

Variable	No of patients†	OS % (sd)	P
Stage FIGO	137		
I	94	97.3%	0.001
II	8	100%	
III	26	85.6%	
IV	9	61%	
Lymphovascular invasion	125		
Yes	11	100%	<i>0.51</i>
No	114	80.6%	
Complete surgical resection	134		
Yes	114	85.1%	0.002
No	20	73.5%	
Postoperative AFP (ng/mL)	119		
≤ 7	65	97.1%	0.048
> 7	54	86.8 %	
Postoperative LDH	90		
Normal	78	92.2%	<i>0.402</i>
>Normal	12	88.9%	
Postoperative HCG	112		
Normal	111	93.7%	<i>0.8</i>
>3	1	100%	
YST histology	137		
No	92	85.6 %	<i>0.076</i>
Yes	45	95.8%	
Choriocarcinoma histology	136		
No	134	81.4%	0.002
Yes	2	50%	

* Survival data is available for 137 patients only

† data is missing for lymphovascular invasion (n=12), modality of surgery (n=3), postoperative AFP (n=18), LDH (n=47) and HCG (n=25), choriocarcinoma histology (n=1)

SD : standard deviation