



## **Need for risk-adapted therapy for malignant ovarian germ cell tumors: A large multicenter analysis of germ cell tumors' patients from French TMRG network**

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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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## Abstract

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

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

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

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

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

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## Introduction

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

International guidelines for treatment of women with MOGCT recommend in most cases fertility-sparing surgery followed by 3-4 cycles of bleomycin, etoposide, and cisplatin (BEP) adjuvant chemotherapy, even in early stages [1, 3, 4]. The current treatments result in at least 90% of overall survival (OS) in women with early stage MOGCT and to up to 80% of OS in patients with advanced disease [3, 5]. Almost 60-70% patients with MOGCT are diagnosed at an early stage (stage I) and adjuvant chemotherapy for these patients remains debatable [6]. So far, no consensus was reached for these patients and more detailed paediatrics and adult's guidelines are still awaited. On the one hand, recommend adjuvant chemotherapy for all MOGCT reduces the risk of recurrence and results in improve EFS even for early stages. But, sparing adjuvant chemotherapy in patients at increased risk of relapse may subsequently correlate with an increased risk of mortality or fertility issues. On the other hand, systematic adjuvant chemotherapy may result in improper overtreatment 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

## **Patients and methods**

### **Data Collection**

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

### **Staging and tumor classification**

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

## **Treatment and follow-up**

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

## **Statistics**

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

## Results

### Patient characteristics and treatment

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

## Outcome

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

## Early stage

In the stage I patient population, the 5y-EFS rates were respectively 94.4% in patients treated with adjuvant chemotherapy ( $N = 59$ ) and 54.6% in patients who underwent surgery followed by surveillance ( $N = 35$ ) ( $P < 0.00001$ ) (Figure 2A). The 5y-OS rates were similar with 96.3% and 97.8% respectively ( $NS$ ) (Figure 2B). In the 17 patients who relapsed, all but 1 underwent chemotherapy. In the 35 patients treated with surgery alone, 13 (37%) relapsed: 6/16 (37.5%) patients with pure dysgerminoma, 3/15 (20%) immature teratoma, 3/3 (100%) YST patients and one (100%) other mixed tumor. All relapsing patients were staged IA patients (Figure 3). Median time to relapse was 11.5 (1-24) months. Eight of the 13 had previous adequate peritoneal staging. Eleven of them received chemotherapy at relapse (1 refused treatment and was lost to follow-up; 1 underwent salvage surgery without chemotherapy). Overall, 11/12 patients were successfully treated at relapse (one

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

### **Advanced stage**

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

### **Prognostic factors**

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

## Discussion

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

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

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

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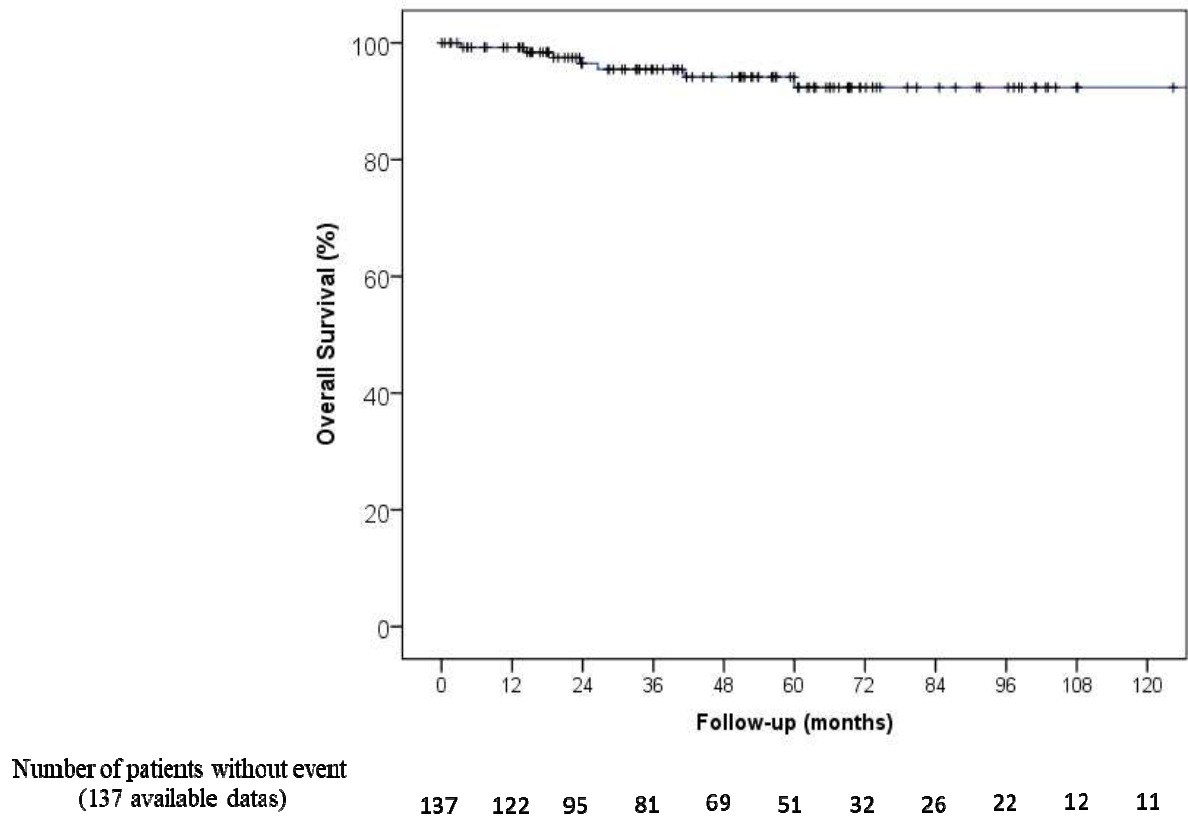
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437

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

A) Overall Survival



B) Event Free Survival

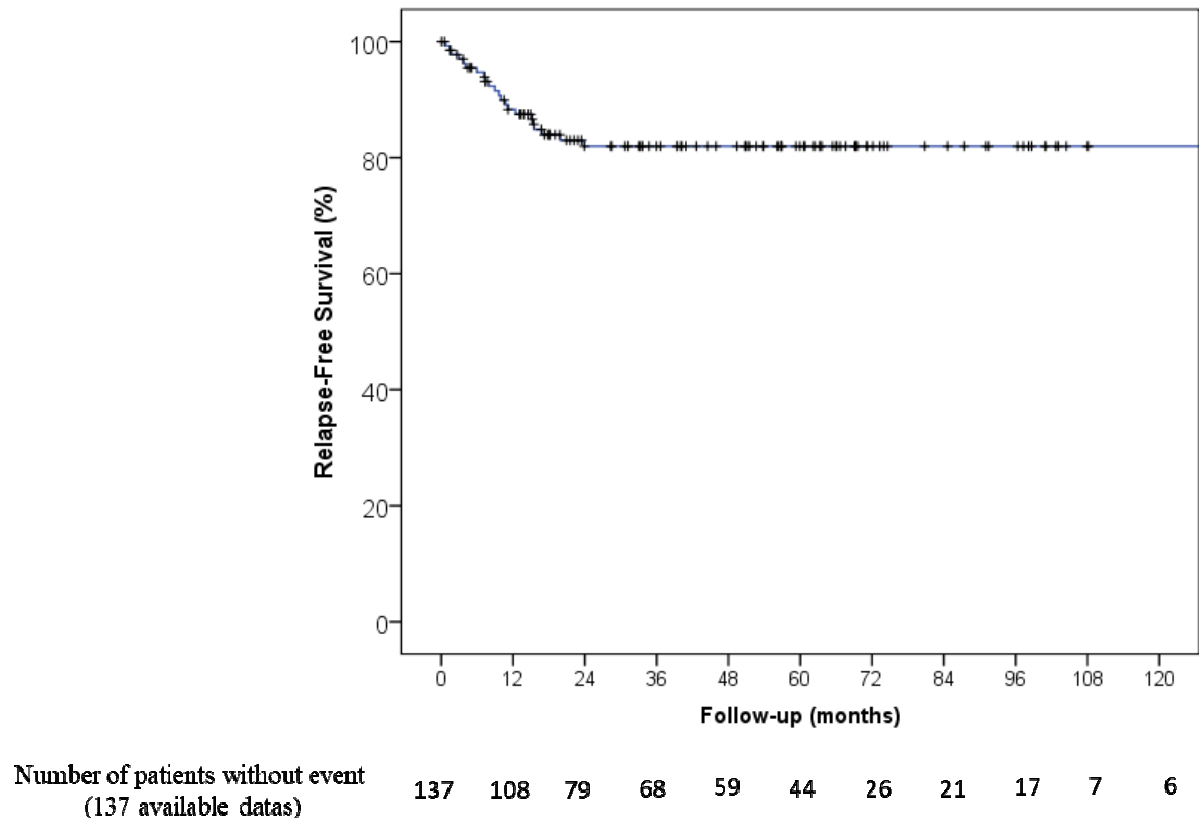
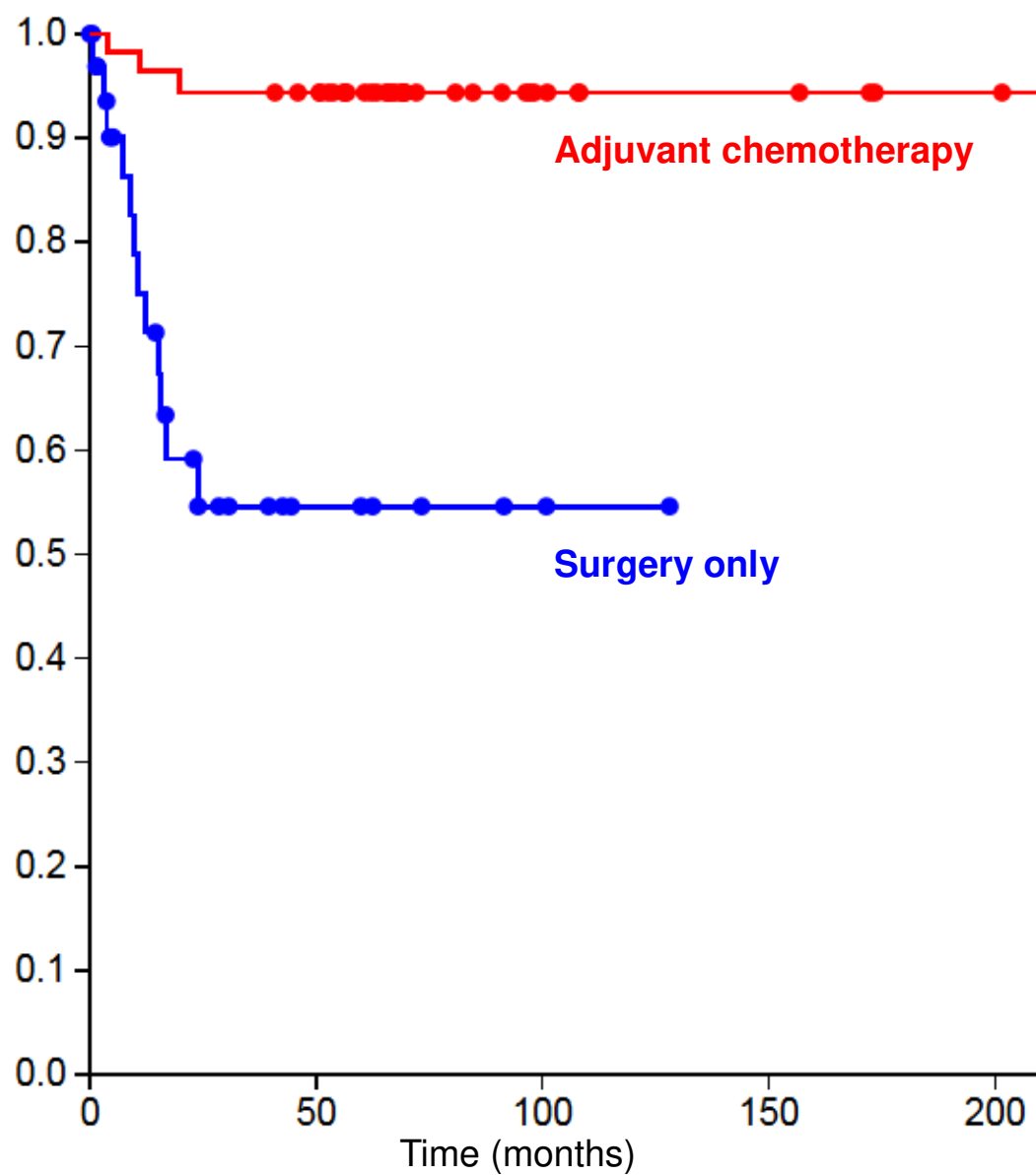


Figure 2– Kaplan Meier Estimates of Event Free Survival (A) and Overall Survival (B) according to adjuvant CT or surveillance following initial surgery in stage I disease

(A) Event Free Survival



(B) Overall Survival

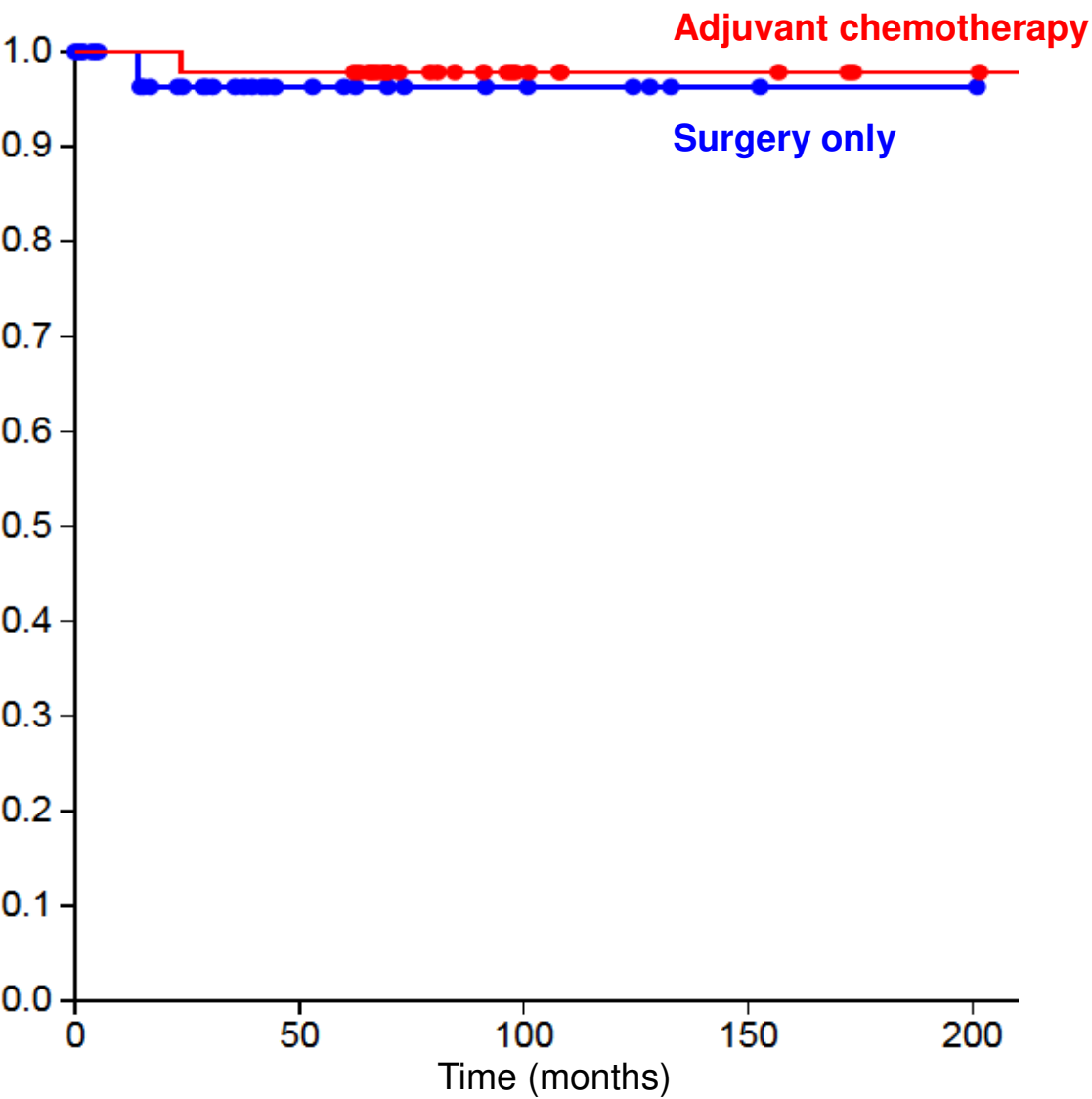
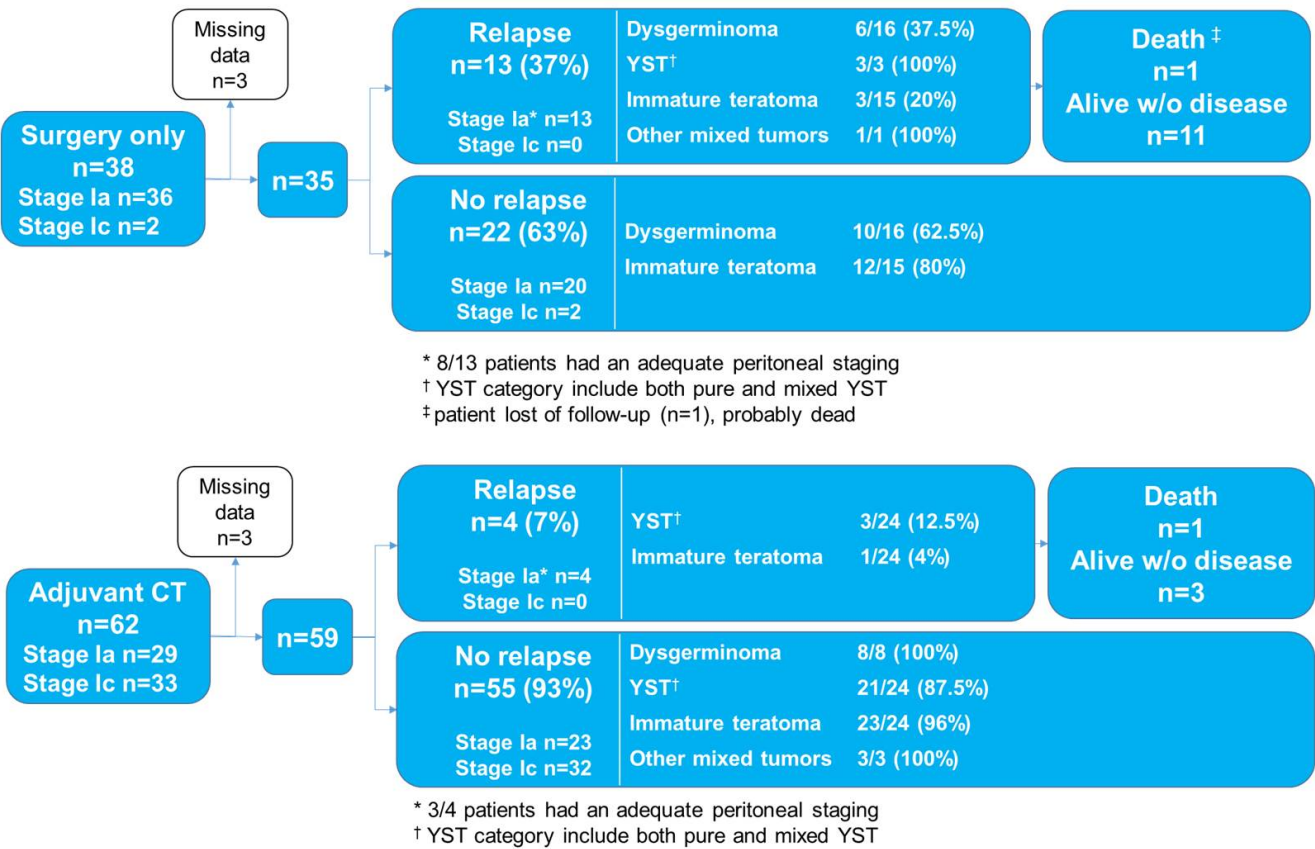
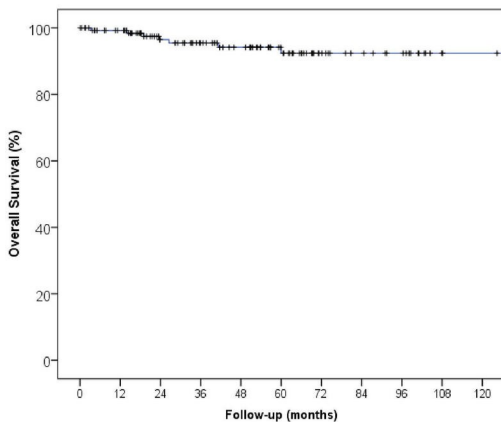


Figure 3– Outcome according to adjuvant chemotherapy or surveillance following initial surgery for stage I MOGCT

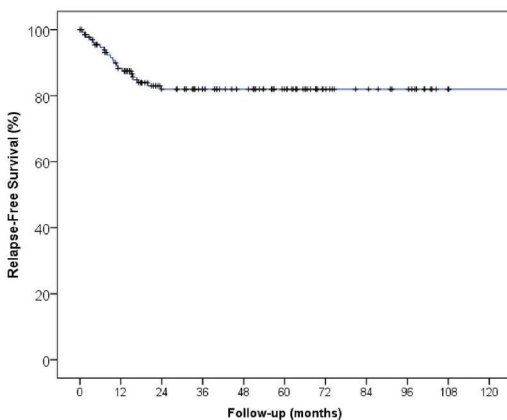
Outcome according to adjuvant chemotherapy (CT) or surveillance following initial surgery





Number of patients without event  
(137 available datas)

137 122 95 81 69 51 32 26 22 12 11

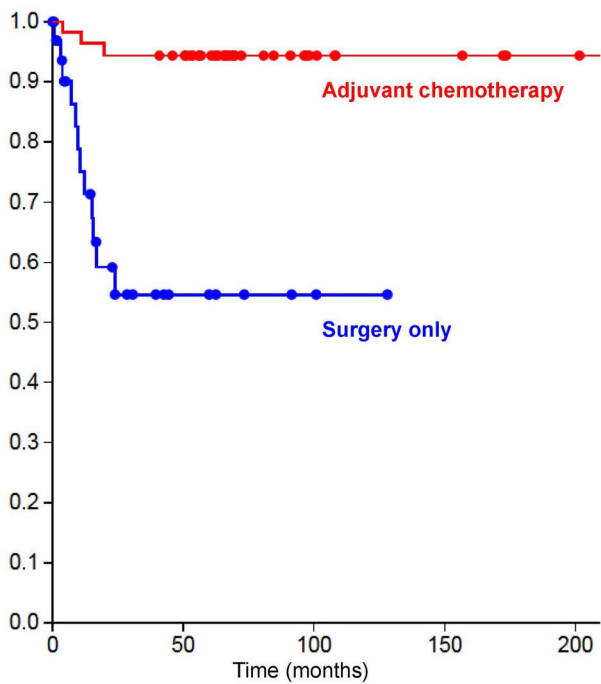


Number of patients without event  
(137 available datas)

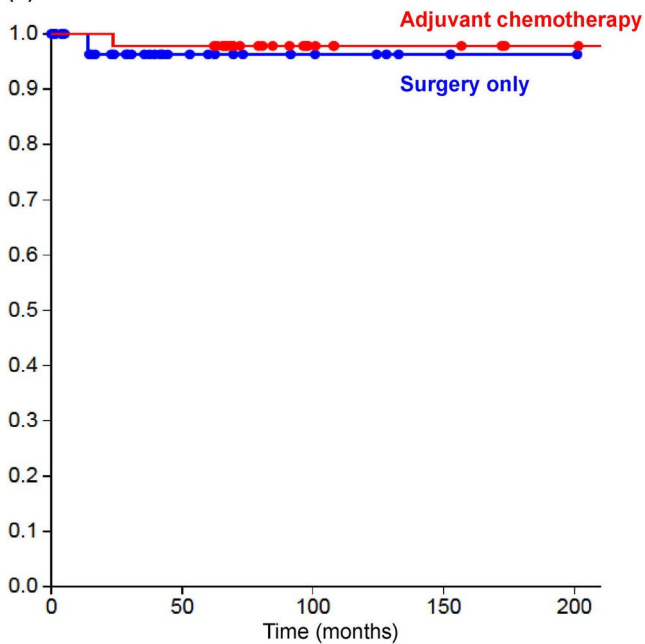
137 108 79 68 59 44 26 21 17 7 6

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

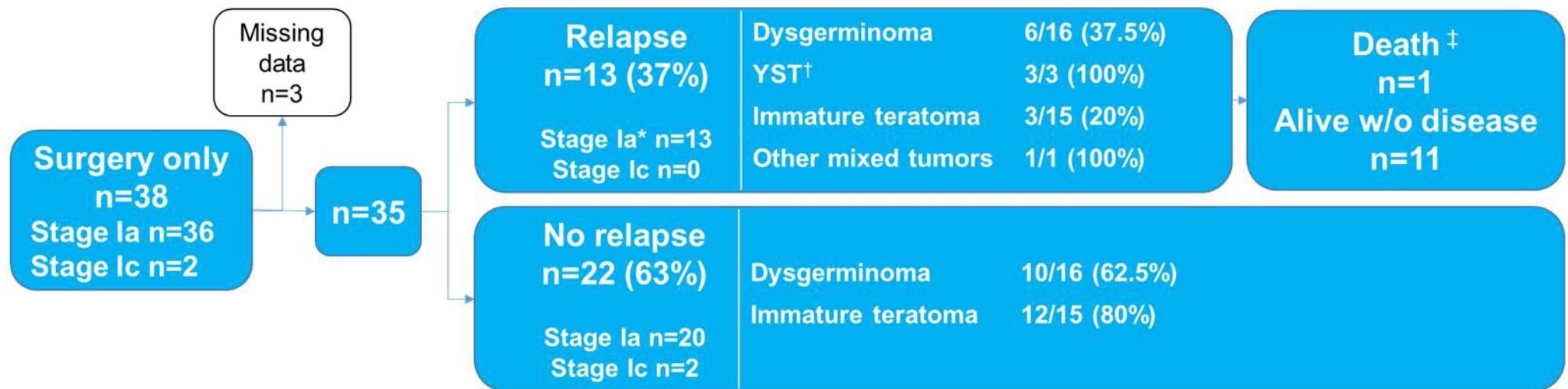
(A) Event Free Survival



(B) Overall Survival



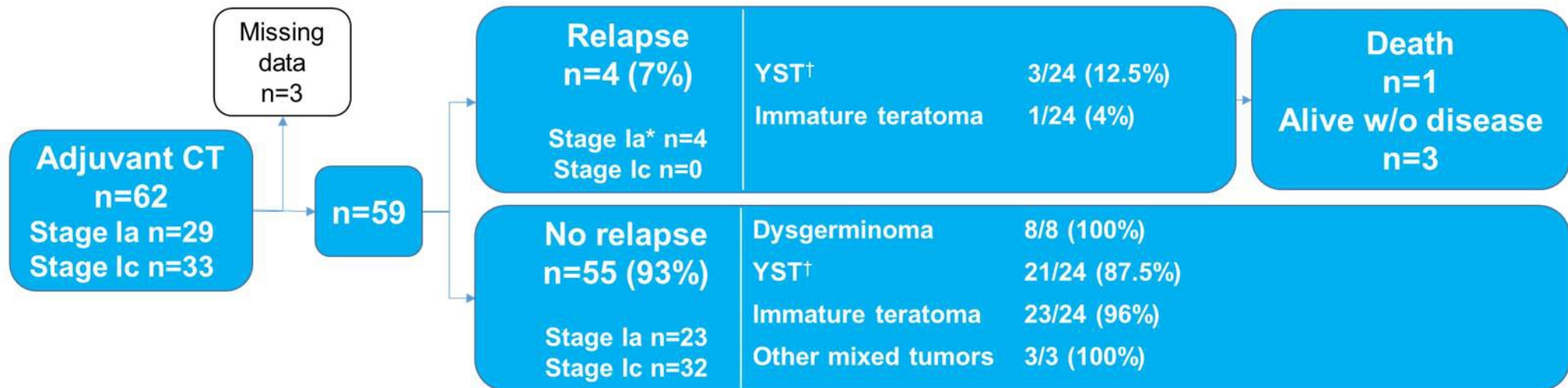
# Outcome according to adjuvant chemotherapy (CT) or surveillance following initial surgery



\* 8/13 patients had an adequate peritoneal staging

<sup>†</sup> YST category include both pure and mixed YST

<sup>‡</sup> patient lost of follow-up (n=1), probably dead



\* 3/4 patients had an adequate peritoneal staging

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