ONLINE COURSE ON RARE FEMALE GENITAL CANCERS.

Germ Cell Ovarian Tumors

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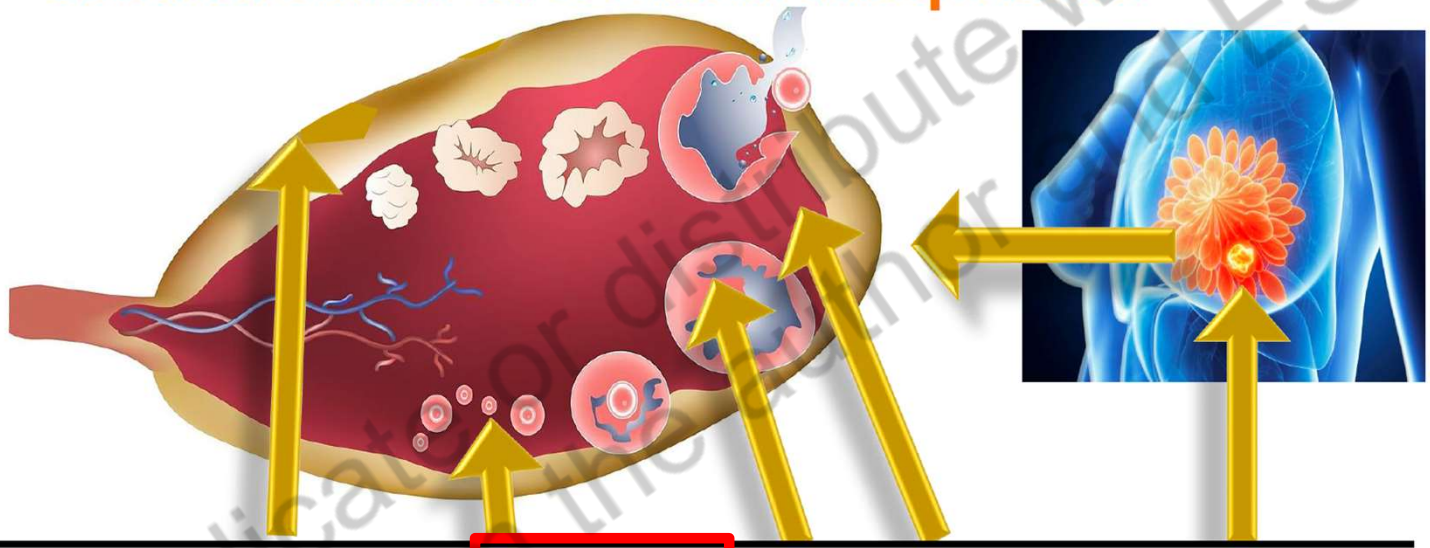
DISCLOSURES

Dr Lorusso received/performed:

- A consulting/advisory role from PharmaMar , Merck Serono, Novartis
- A speakers bureau role from AstraZeneca, Clovis Oncology, PharmaMar, and Tesaro/GSK
- Travel/accommodations/expenses from AstraZeneca, Clovis Oncology, PharmaMar, Roche, and Tesaro/GSK
- Expert testimony on behalf of Clovis Oncology
- Honoraria from AstraZeneca, Clovis Oncology, Genmab, Immunogen, Merck, Roche, and Tesaro/GSK
- Research funding (to institution) from Clovis Oncology, Merck, PharmaMar, and Tesaro/GSK

Classification of Ovarian Neoplasms



Origin	Surface Epithelial Cells	Germ Cells	Sex Cord Stroma	Metastasis to Ovaries
Frequency	65%-70%	15%-20%	5%-10%	5%
Proportion of malignant ovarian tumors	90%	3%-5%	2%-3%	5%
Age group affected	30+	0-25+	All ages	Variable

DIAGNOSIS AND PATHOLOGY

SPECIAL SERIES: ADVANCES IN THE MANAGEMENT OF GYNECOLOGIC CANCERS

Management of Rare Ovarian Cancer Histologies

David M. Gershenson, MD[1]; Aikou Okamoto, MD, PhD[2]; and Isabelle Ray-Coquard, MD, PhD[3]

Symptoms	% of pts
Abdominal pain+palpable pelvic-abdominal mass	85%
Acute abdominal pain caused by rupture, hemorrhage, or torsion	10%
Abdominal distention	35%
Fever	10%
Ascites	10%
Vaginal bleeding	10%

LARGE TUMOR SIZE + YOUNG PATIENT AGE

REVIEW ARTICLE

Gynecologic Cancer Intergroup (GCIG) Consensus Review for Ovarian Germ Cell Tumors

Jubilee Brown, MD, Michael Friedlander, MBChB, FRACP, PhD,† Floor J. Backes, MD,‡ Philipp Harter, MD,§ Dennis M. O'Connor, MD,|| Thibault de la Motte Rouge, MD,¶ Domenica Lorusso, MD,# Johanne Maenpaa, MD,** Jae-Weon Kim, MD, PhD,†† Meghan E. Tenney, MD,‡‡ and Michael J. Seckl, PhD, FRCP§§*

IMAGING

- Alotaibi et al, 2010: all **solid tumors** were immature teratomas at US
- Benign cystic teratomas are more commonly **cystic** (77% vs 18%) and **smaller** (7.7 vs 16.9 cm; $p < 0.001$)

Evaluation of Extra-ovarian Disease

- CT or MRI of chest
- MRI of the brain if supradiaphragmatic disease or choriocarcinoma

DIAGNOSIS AND PATHOLOGY

	Tumor Marker		
Tumor	AFP	β-hCG	Lactic dehydrogenase
Pure dysgerminoma	Normal	May be elevated	Elevated
Immature teratoma	May be elevated	Normal	Normal
Endodermal sinus tumor	Elevated	Normal	May be elevated
Embryonal carcinoma	Elevated	Elevated	Elevated
Choriocarcinoma	Normal	Elevated	Normal

Markers may suggest individual tumor subtypes

LDH and CA-125 can be elevated but nonspecific:
→useful during FUP

"Diagnostic work-up should include pelvic US, abdomino-pelvic CT scan, chest X-ray **and PET scan in selected cases (GCTs) [III, B]".**

SURGICAL STAGING (PERITONEAL)

ESMO

Annals of Oncology 28: 333–338, 2017
doi:10.1093/annonc/mdw563
Published online 1 November 2016

ORIGINAL ARTICLE

The role of staging and adjuvant chemotherapy in stage I malignant ovarian germ cell tumors (MOGTs): the MITO-9 study

G. Mangili[1], C. Sigismondi[1*], D. Lorusso[2], G. Cormio[3], M. Candiani[1], G. Scarfone[4], F. Mascilini[5], A. Gadducci[6], A. M. Mosconi[7], P. Scollo[8], C. Cassani[9], S. Pignata[10] & G. Ferrandina[11]

Table 2. Cox's regression analysis of risk factors for recurrence

Factor	N.	Recurrence rate (%)	P value (Cox regression)	OR 95% CI
Fertility sparing	21	16.8	0.353	1.99 (0.46–8.55)
Radical surgery	2	10.5		
Adjuvant chemotherapy	9	18.6	0.209	1.71 (0.74–3.95)
Surgery alone	14	12.2		
Standard treatment	12	10	0.117	1.93 (0.84–4.4)
Surveillance	11	25.6		
Peritoneal staging	**10**	**8.6**	**0.04**	**2.37 (1.04–5.44)**
No staging	**13**	**26**		
Stage IA–IB	12	13	0.144	1.87 (0.8–4.32)
Stage IC	11	21.1		
Yolk sac/mixed	5	17.1	0.439	1.48 (0.55–3.98)
Other histologies	18	12.8		

Peritoneal staging versus No staging is the only independent risk factor for recurrence ($P<0.05$).

Table 1. Clinico-pathological patient features and treatment strategies

Clinico-pathological characteristics		Stage	No. (%)
Histology	Dysgerminoma (N=55)	IA	18 (12.5)
		IB	3 (2.1)
		IC	16 (11.1)
		Ix	18 (12.5)
	Immature teratoma (N=49)	IA	22 (15.3)
		IB	2 (1.4)
		IC	12 (8.3)
		Ix	13 (26.5)
	Yolk sac tumors (N=26)	IA	10 (6.9)
		IC	13 (9.0)
		Ix	3 (2.1)
	Mixed (N=14)	IA	5 (3.5)
		IC	6 (4.1)
		Ix	3 (2.1)
Treatmentstrategies			
Site of primary surgery	MITO centers		93 (64.6)
	Elsewhere		51 (35.4)
Surgical treatment	Fertility sparing		125 (86.8)
	Radical surgery		19 (13.2)
Peritoneal staging	No		50 (34.7)
	Yes		94 (65.3)
Lymph node staging	No		99 (68.7)
	Yes		45 (31.2)
Adjuvant chemotherapy	No		71 (49.3)
	Yes		73 (50.7)
Total			144 (100)

- Yolk sac is predictor for survival
- **OS 96.8% and 88.7% surgically staged/incomplete staged arm**
- OS 93.8% and 94.1% in standard treatment and surveillance arm

ESMO

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SURGICAL MANAGEMENT

NON-FERTILITY SPARNG

In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy could be carried out with careful surgical staging

FERTILITY SPARNG (also in advanced disease)

Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is now considered as the standard surgical treatment for young patients with GCTs

Conservative Surgery to Preserve Ovarian Function in Patients with Malignant Ovarian Germ Cell Tumors

A Review of 74 Cases

Systematic ovarian biopsy is not necessary when the contralateral ovary is macroscopically normal [III, A].

Contents lists available at ScienceDirect

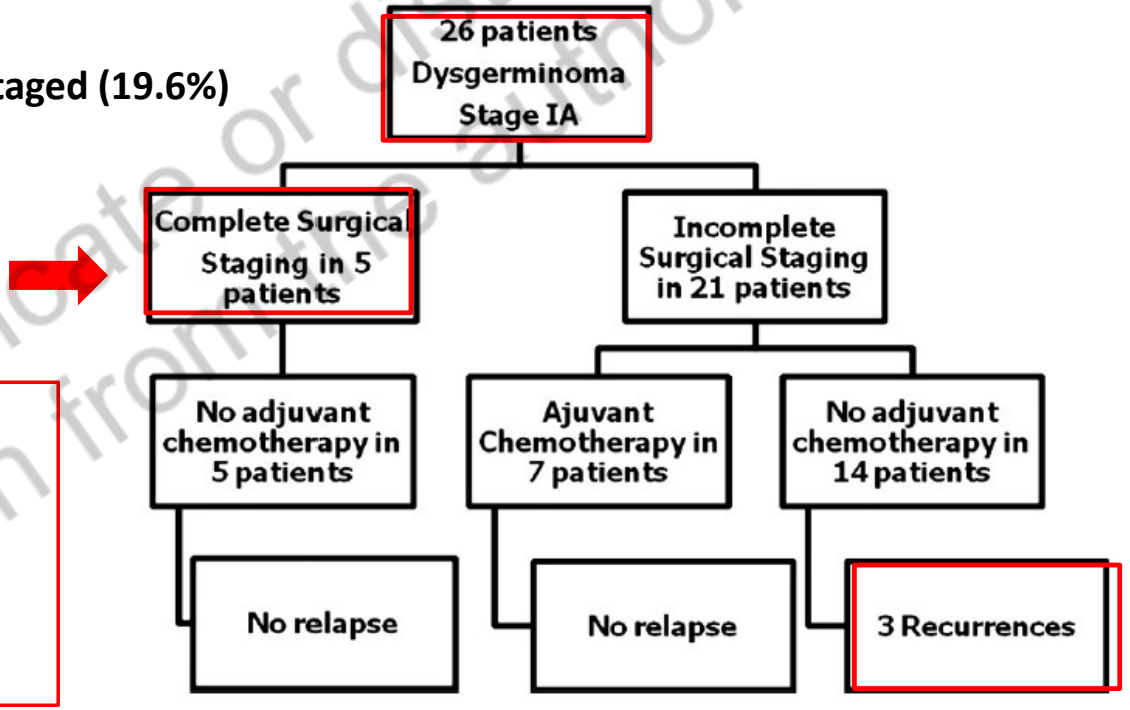
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Is surgical restaging indicated in apparent stage IA pure ovarian dysgerminoma? The MITO group retrospective experience

G. Mangili [a,*], C. Sigismondi [a], D. Lorusso [b], G. Cormio [c], P. Scollo [d], R. Viganò [a], T. Gamucci [e], M. Candiani [a], S. Pignata [f]

Only 5 pts completely staged (19.6%)



3 RECURRENCES

1) **None** of them was **completely stage**
2) **None** of them had received **adjuvant treatment**

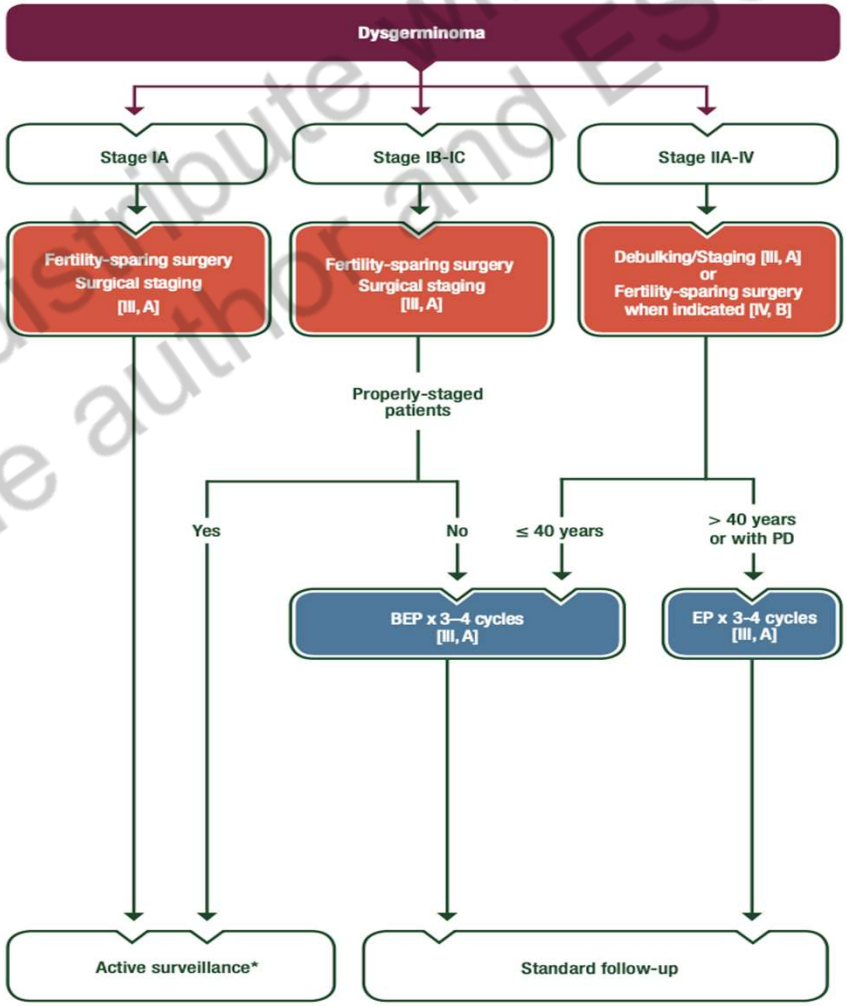
Management of early stage Disgerminoma

Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

I. Ray-Coquard[1], P. Morice[2], D. Lorusso[3], J. Prat[4], A. Oaknin[5], P. Pautier[2] & N. Colombo[6], on behalf of the ESMO Guidelines Committee*

- Stage IA Disgerminoma should be treated with surgery alone
- The recurrence rate is relatively low (15%-25%)
- Patients can be successfully treated at the time of relapse with a high likelihood of cure

Adjuvant chemotherapy in stage IB-IC is recommended, but active surveillance can be an option if patients are properly staged



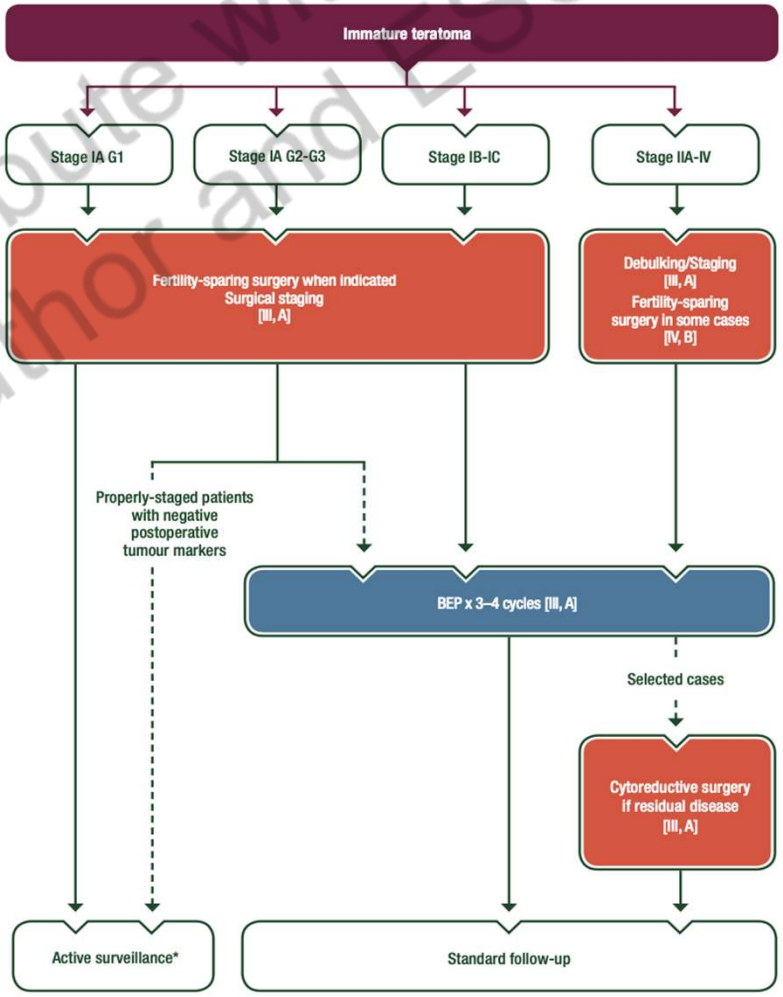
Management of early stage Immature Teratoma

Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

I. Ray-Coquard[1], P. Morice[2], D. Lorusso[3], J. Prat[4], A. Oaknin[5], P. Pautier[2] & N. Colombo[6], on behalf of the ESMO Guidelines Committee*

Patients with stage IA G1 immature teratoma do not require further chemotherapy after complete surgical staging

The need for adjuvant CT in stage IA G2-G3, properly staged and with negative postoperative tumor biomarkers is still controversial and active surveillance can be proposed



Management of early stage Immature Teratoma

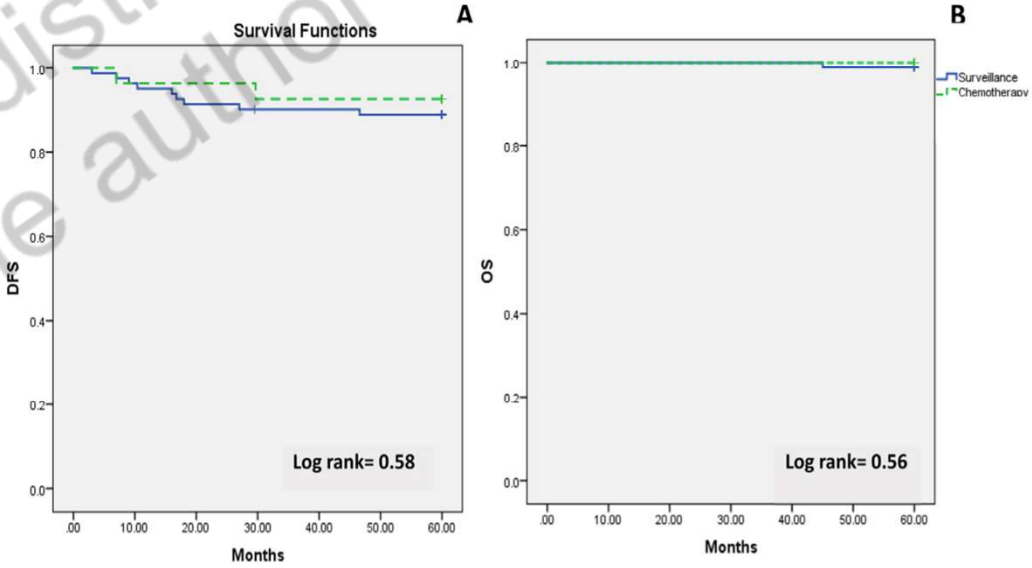
Can we replace adjuvant chemotherapy with surveillance for stage IA-C immature ovarian teratomas of any grade? an international multicenter analysis

Alice Bergamini [a,b,*], Naveed Sarwar [c], Gabriella Ferrandina [d,e], Giovanna Scarfone [f], Dee Short [c], Xianne Aguiar [c], Cristina Camnasio [g], Baljeet Kaur [c], Philip M. Savage [h], Gennaro Cormio [i], Adrian Lim [j], Sandro Pignata [k], Giorgia Mangili [a], Michael J. Seckl [c,**]

Table 1
Clinicopathological characteristics of patients.

Patients characteristics	Surveillance N = 81 (75%)	Chemotherapy N = 27 (25%)	P	Total N = 108
Age (years)			0.78	
Mean ± SD (range)	26.7	27.2		26.9 (16 −51)
Stage			<0.05	
IA G1	21 (25.9%)	1 (3.7%)		22 (20.4%)
IA G2	22 (27.2%)	1 (3.7%)		23 (21.3%)
IA G3	14 (17.3%)	7 (25.9%)		21 (19.4%)
IB G1	1 (1.2%)	0		1 (0.9%)
IB G2	1 (1.2%)	0		1 (0.9%)
IB G3	0	1 (3.7%)		1 (0.9%)
IC G1	8 (9.9%)	0		8 (7.4%)
IC G2	10 (12.4%)	7 (25.9%)		17 (15.7%)
IC G3	4 (4.9%)	10 (37.1%)		14 (13.0%)
Type of surgery			0.41	
Fertility sparing	76 (93.8%)	24 (88.9%)		100 (92.6%)
Radical	5 (6.2%)	3 (11.1%)		8 (7.4%)
Complete staging			0.80	
	59 (72.8%)	21 (77.0%)		80 (74%)

SD = standard deviation; G1 = grade 1; G2 = grade 2; G3 = grade 3.



No. At risk

Surveillance	81	78	74	72	72	71	71
Chemotherapy	27	26	26	25	25	25	25

No. At risk

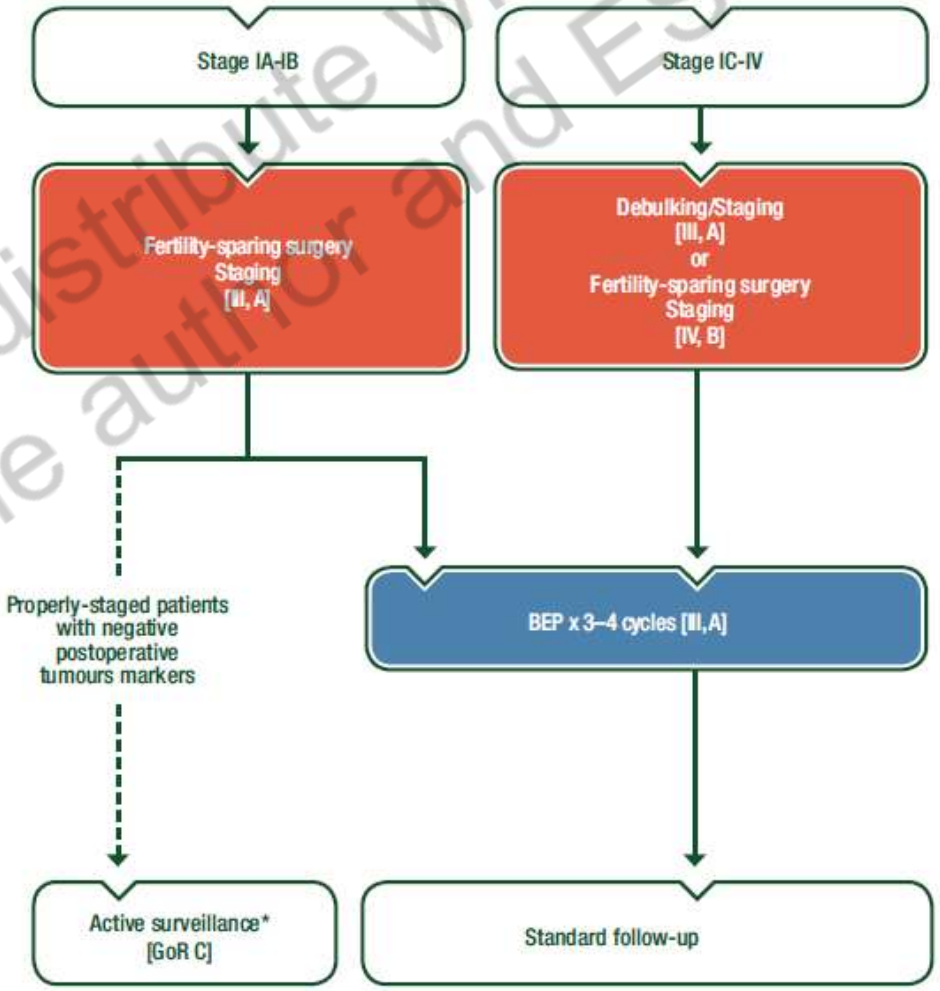
	81	81	81	81	81	80	80
	27	27	27	27	27	27	27

Management of early stage Yolk sac tumor

Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

I. Ray-Coquard[1], P. Morice[2], D. Lorusso[3], J. Prat[4], A. Oaknin[5], P. Pautier[2] & N. Colombo[6], on behalf of the ESMO Guidelines Committee*

Adjuvant chemo is the standard of care in all stage Yolk Sac tumors, but in stage IA-IB **surveillance in an option in properly staged patients** with negative postoperative tumor markers



Active surveillance

Surveillance schedule involving clinical examination, abdomen-pelvic sonography and tumour markers, with a gradual increase of the interval between clinical appointments

Table 5. Active surveillance programme in the management of ovarian GCTs

Time period	Examination	Pelvic US	Tumour markers	Chest X-ray	CT chest abdomen pelvis
1st year	monthly	2 monthly	every 2 weeks (first 6 months) and then monthly	2 monthly	1 month[a] 3 months[b] 12 months
2nd year	2 monthly	4 monthly	2 monthly	4 monthly	
3rd year	3 monthly	6 monthly	3 monthly	6 monthly	
4th year	4 monthly		4 monthly	8 monthly	
5th to 10th year	6 monthly		6 monthly	annually	

ESMO guidelines, 2018

Management of advanced stage

- Fertility-sparing surgery should be considered also in advanced stages

- Platinum-based regimens are the treatment of choice

BEP (Bleomicin/Etoposide/Cisplatin)
Is the most used regimen!

Optimal number of cycles of BEP has not been established in RCT.
Reccommendations:

- **4 cycles of BEP for advanced disease (only 3 with bleomicin for lung toxicity)**

- **3 cycles of BEP for completely resected/stage I tumors might be an option**

Management of recurrent disease

- Most patients are cured; few patients relapse-most relapses occur within 24 months
- Data for salvage therapy are scarce, extrapolated from the experience in testis cancer
- Most important prognostic factor: resistance to platinum

  Recurrence < 4-6 weeks: platinum resistant (long term survival ~5-15%)

  Recurrence > 4-6 weeks: platinum sensitive (long term survival >50% with reintroduction of platinum based CT)

CISPLATIN RESISTANT PATIENT

- Vincristine/actinomycin D/cyclophosphamide
- Paclitaxel/gemcitabine
- Gemcitabine/ oxaliplatin

CISPLATIN SENSITIVE PATIENT

- Ifosfamide/platinum (IP) +/-paclitaxel

OR

- vinblastine/ifosfamide/cisplatin (VeIP) and cisplatin/vinblastine/ bleomycin (PVB)

Management of recurrent disease: High dose CT with stem cell rescue might be an option

13 patients treated with Carboplatin 700mg/m2 and etoposide 750mg/m2 intravenously (i.v.) daily for 3 consecutive days followed by stem cell infusion

High-Dose Chemotherapy for Recurrent Ovarian Germ Cell Tumors

Table 1. Patient Characteristics

Patient No.	Age at HDCT (years)	Histology	No. of Prior Treatments	Prior Nonsurgical Treatments	Platinum Refractory	Sites of Metastases at HDCT	Tumor Markers at HDCT	Outcomes	Survival (months)
1	27	Yolk sac	1	EP × 4	No	Pelvis	AFP-300, HCG-1	CR	+120 cNED
2	39	NG-chorio	1	BEP × 3	No	Lungs	HCG-1384, AFP- 1	CR-relapse in 4 months	11 DOD
3	26	Yolk sac	1	BEP × 3	No	Liver, retroperitoneum	AFP-1541, HCG-1	CR	+ 22 cNED
4	33	Yolk sac	1	BEP × 5	Yes	Liver, peritoneum	AFP-6067, HCG-1	CR	+12 cNED
5	21	Yolk sac	1	BEP × 3 + EP × 1	Yes	Pelvis, retroperitoneum	AFP-1021, HCG-1	PD	11 DOD
6	33	Yolk sac	2	BEP × 3, VAC × 4	No	Peritoneum	AFP-22, HCG-1.5	CR	+ 270 cNED
7	17	Yolk sac	2	BEP × 6, VIP × 1	Yes	Liver	AFP-2095, HCG-1	sCR, PD on imaging	8 DOD
8	24	Yolk sac	2	Radiation, BEP × 4	Yes	Bone, lungs, mediastinum, retroperitoneum	AFP-4780, HCG-125	PD	4 DOD
9	14	Yolk sac	2	BEP × 5, VeIP × 4	Yes	Retroperitoneum	AFP- 562, HCG-1.9	CR-relapse in 4 months	8 DOD
10	16	Yolk sac	2	BEP × 5, ICE × 1	Yes	Lungs, retroperitoneum	AFP-538, HCG-1	sCR, PD on imaging	13 DOD
11	26	Yolk sac	3	EP × 4, EP × 4, BEP × 2	No	Pelvis	AFP-49.7, HCG-1	CR-relapse in 6 months	33 DOD
12	20	Yolk sac	3	BEP × 3, BEP × 3 + EP × 3, taxol + gemcitabine × 1	Yes	Liver, peritoneum, supraclavicular lymph node	AFP-64004, HCG-3.1	PD	8 DOD
13	47	NG-chorio	4	EMA-CO, BEP × 4, VAC × 3, EMA-EP	Yes	Retroperitoneum, pelvis	AFP-2.5, HCG-5746	sCR, PD on imaging	6 DOD

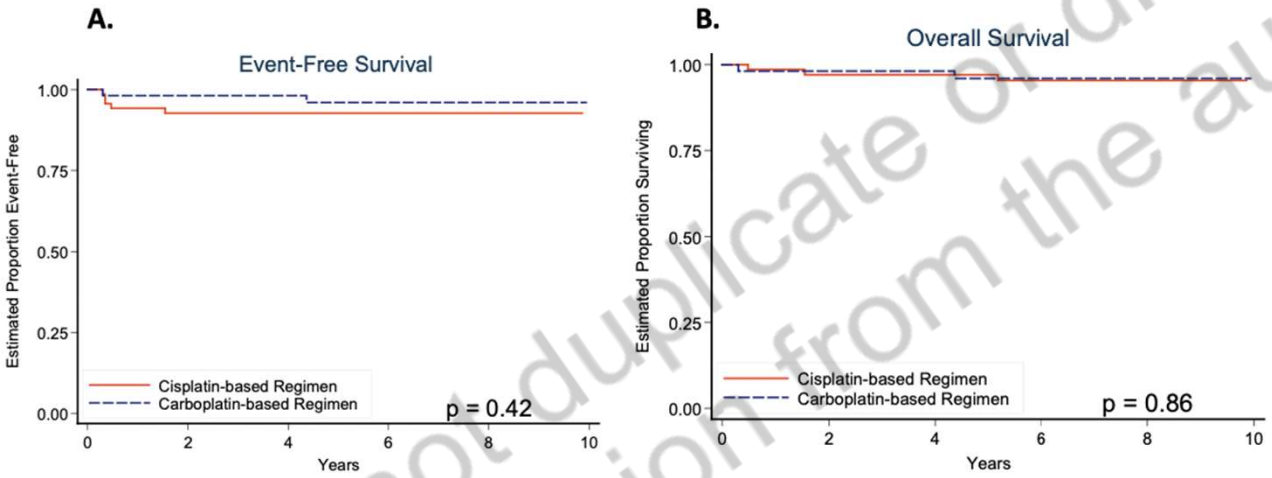
7/13 pts achieved CR

4 pts disease free at 12, 22, 120 and 270 months

Carboplatin as an alternative

Is carboplatin-based chemotherapy as effective as cisplatin-based chemotherapy in the treatment of advanced-stage dysgerminoma in children, adolescents and young adults?

Rachana Shah [a,*], Caihong Xia [b], Mark Krailo [b,c], James F. Amatruda [d], Suren G. Arul [e], Deborah F. Billmire [f], William E. Brady [g], Allan Covens [h], David M. Gershenson [i], Juliet P. Hale [j], Jean Hurteau [k], Matthew J. Murray [l],



126 patients treated:
- 56 pts received carboplatin-based CT
- 70 pts received cisplatin-based CT

Carboplatin-based regimen in the frontline treatment of all patients with advanced-stage disgerminoma minimizes treatment-related toxicity

Shah R, Gynecol Oncol, 2018

The role of SECONDARY SURGERY

ESMO

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CLINICAL PRACTICE GUIDELINES

Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

I. Ray-Coquard[1], P. Morice[2], D. Lorusso[3], J. Prat[4], A. Oaknin[5], P. Pautier[2] & N. Colombo[6], on behalf of the ESMO Guidelines Committee*

The role of secondary cytoreductive surgery for pts with recurrent or progressive GCT **remains controversial**

However…

A. "Any resectable residual disease should be removed, particularly if normal serum marker after adjuvant therapy and for immature teratoma"

A. Unlike males, females who have a relapse with malignant disease after primary ChT for GCTs have a **poor prognosis**

Conclusions

- MOGCT are rare tumours, usually occurring in young women, with an excellent prognosis.
- Fertility sparing surgery should be considered for all patients who desire to retain fertility, regardless the stage of disease.
- Major cytoreductive surgery is usually limited to those patients with residual disease after chemotherapy.
- Close surveillance is increasingly being offered to patients with properly staged stage 1 disease and negative postoperative biomarkers
- BEP chemotherapy is the most commonly used chemotherapy regimen
- Patients relapsing after chemotherapy remain a major challenge, as they have lower cure rates than their male counterparts.