



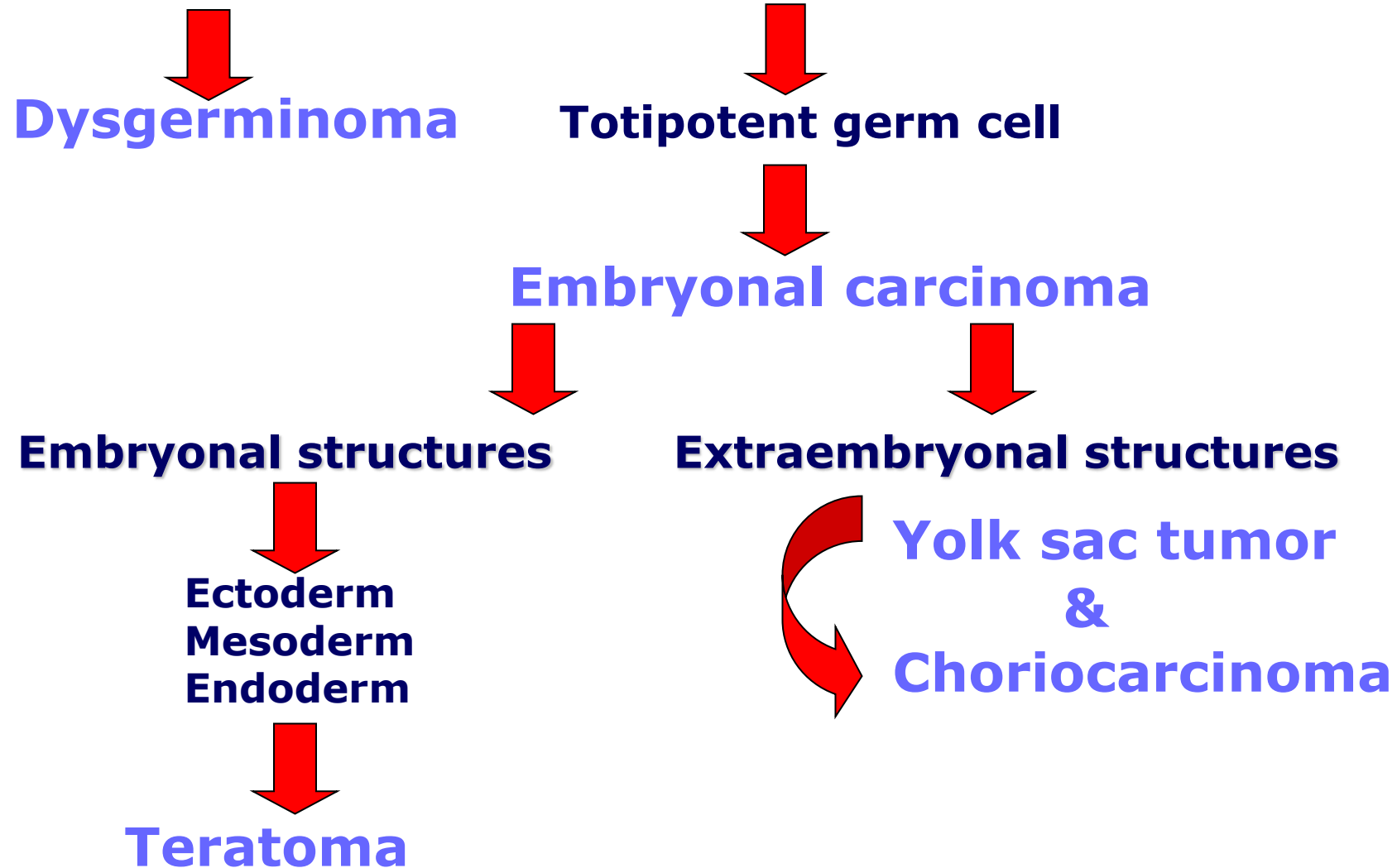
Malignant Ovarian Germ Cell Tumors

Nicoletta Colombo

Ovarian Germ Cell Tumors

- ❑ 5% of all ovarian malignancies
 - ❑ Usually in adolescents or young adults
 - ❑ 60-70% STAGE 1 at diagnosis, despite very aggressive
 - ❑ Highly chemo-responsive and curable
 - ❑ No randomized trials in OGCT, extrapolation from randomized trials in testis cancer
-

Primordial germ cell



Ovarian Germ Cell Tumours

- ☐ Dysgerminoma
 - ☐ Yolk sac tumour
 - ☐ Embryonal Carcinoma
 - ☐ Non Gestational Choriocarcinoma
 - ☐ Mixed germ cell tumour (specify components)
 - ☐ Teratoma-Mature/Immature
 - Immature – low grade/high grade
 - ☐ Monodermal teratoma and somatic-type tumours arising from a dermoid cyst
-

General features of MOGCTs

- ❖ **Rare**= send to referral centers
- ❖ **Young**= spare fertility
- ❖ **Aggressive**= often treated in emergency Units
- ❖ **Chemosensitivity**= hold any demolitive procedure



Clinical Presentation

- ❑ Rapidly growing pelvic mass
 - ❑ Subacute pelvic pain, feeling of pelvic pressure
 - ❑ Acute abdomen, secondary to torsion, necrosis or rupture of the ovarian tumor, can be the first clinical manifestation in a teenager
-

Serum markers in MOGCTs

Tumor markers are excellent for diagnosis and management of MOGCTs, used to check for complete remission or recurrence

	AFP	HCG	CA125	CA19.9	LDH
Choriocarcinoma	-	+	-	-	-
Yolk Sac Tumor	+	-	-	-	-
Dysgerminoma	-	±	±	-	+
Immature teratoma	±	-	±	±	-
Mixed GCT	±	±	±	±	±

Surgical Treatment

- ✓ Pre-operative markers (AFP, β hCG, LDH)
 - ✓ **Fertility-sparing surgery**
 - ✓ Careful inspection of peritoneum, omentum, contralateral ovary and nodes, washings and biopsies of suspicious areas
 - ✓ Unilateral oophorectomy with “moderate” debulking if advanced stage
-

Dysgerminomas: is restaging of IA tumors always

Gynecologic Oncology 121 (2011) 280–284



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

^a Gynecology Department, I.R.C.C.S. San Raffaele Hospital, Milan, Italy

^b Gynecologic Oncology Unit, Catholic University of the Sacred Heart, Rome, Italy

^c Gynecologic Oncology Unit, Department of Gynecology, Obstetrics and Neonatology, University of Bari, Bari, Italy

^d Obstetrics and Gynecology Department, Cannizzaro Hospital, Catania, Italy

^e Oncology Department, Ospedale SS Trinità, Sora, Rome, Italy

^f Gynecologic Oncology Department, National Cancer Institute, Naples, Italy

Dysgerminomas: is restaging of IA tumors always necessary?

After a median FUP of 100 months, all patients are alive and NED

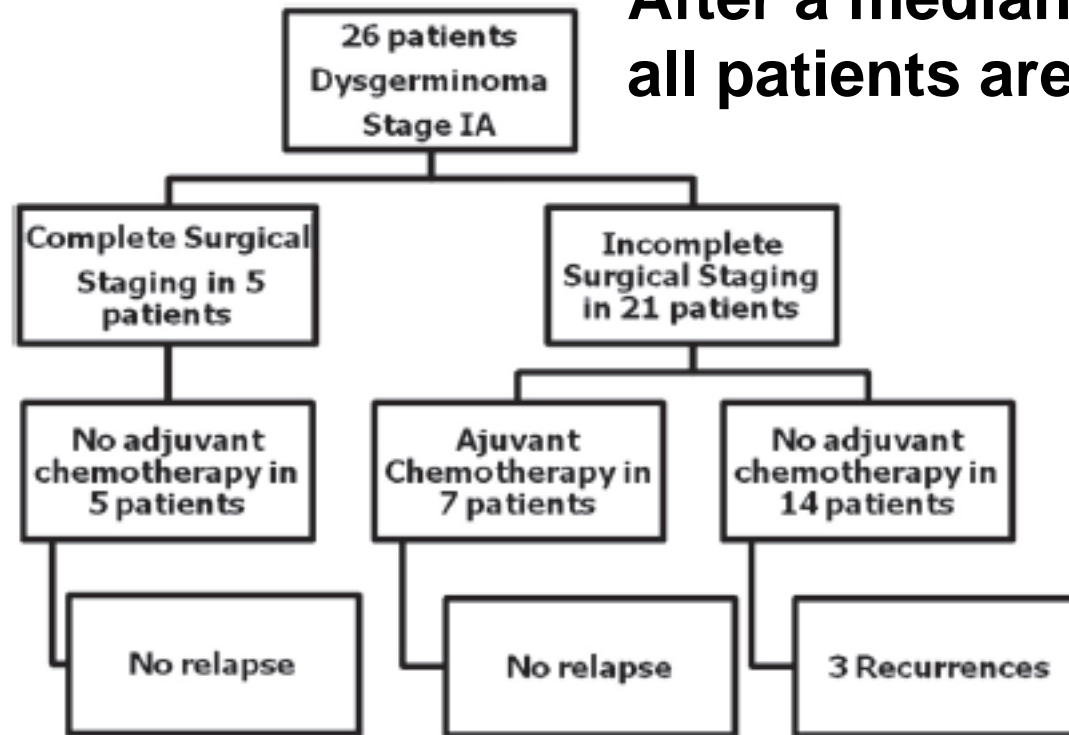


Fig. 1. Clinical management of 26 patients affected by pure ovarian dysgerminoma.

Adjuvant Chemotherapy

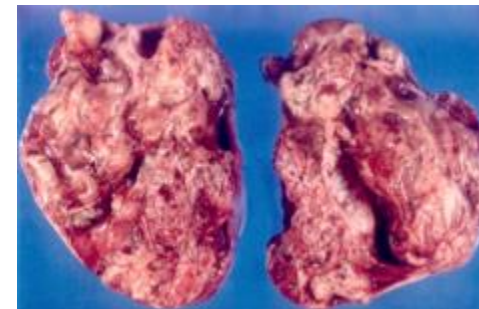
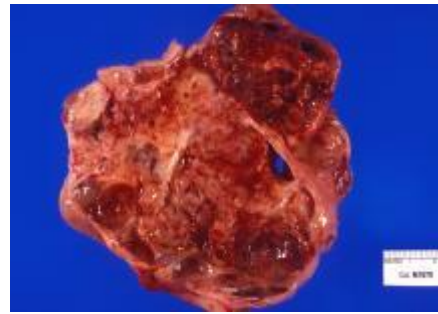
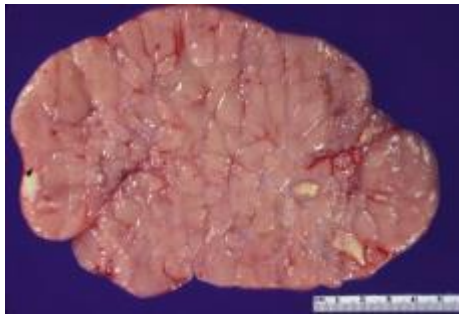
When?
Which?

The Importance of Histology

DYSGERMINOMAS

NON-DYSGERMINOMAS

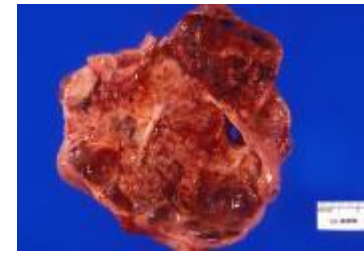
IMMATURE TERATOMAS, YOLK SAC TUMORS, MIXED TUMORS



Management of Dysgerminomas

- ❑ Most patients Stage 1a- surveillance appropriate.
 - ❑ 15% will relapse and salvaged with chemotherapy
 - ❑ Rare-therefore not clear if BEP X 3 is essential-in advanced or recurrent disease
 - ❑ GOG STUDY- 39 patients with stage 1b-3 completely resected-treated with Carboplatin 400mg/m² and etoposide 120mg/m² x3 every 4 weeks x 3 **No recurrences**
-

Non-Dysgerminomas



- ✓ Accurate monitoring of tumor markers (AFP and β hCG)
- ✓ Adjuvant treatment with BEP x 3-4 cycles (according to stage)
- ✓ 5 days BEP less toxic and optimal regimen

**BEP: Bleomycin 30,000 IU D1,8,15; Etoposide 100mg/m²
D1-5; Cisplatin 20mg/m² D 1-5 (BEP) q 3 weeks**

CHEMOTHERAPY – WHEN?

MOGCTs

Historical approach

ADVANCED STAGES DYSGERMINOMA &
IMMATURE TERATOMA

&

ALL STAGES NON DYSGERMINOMATOUS
TUMORS

NEED CHEMOTHERAPY

Recommended regimen - BEP

Toxicity of BEP

- ☐ Pulmonary toxicity 3%; decreased DLCO 20%
 - ☐ AML 0.2- 1%
 - ☐ Neuropathy 20%
 - ☐ Raynauds 20%
 - ☐ Tinnitus 24%
 - ☐ High tone hearing loss 70%
 - ☐ Gonadal dysfunction 16 -30%
 - ☐ Cardiovascular disease/Hypertension
-

Ovarian Germ Cell Tumors

Can stage 1 be managed with close surveillance?

- ❑ Surveillance successful in male germ cell tumours
 - 20-30% relapse but salvaged
 - 2 cycles of BEP in “high risk”

 - ❑ What about ovarian germ cell tumours ?
-

Early stages Germ cell tumors Surveillance or chemotherapy?

Int J Gynecol Cancer 2008, **18**, 43–50

A review of the close surveillance policy for stage I female germ cell tumors of the ovary and other sites

D.M. PATTERSON*, N. MURUGAESU†, L. HOLDEN†, M.J. SECKL† & G.J.S. RUSTIN*

**Department of Medical Oncology, Mount Vernon Hospital, Northwood, Middlesex, United Kingdom; and*

†Department of Medical Oncology, Charing Cross Hospital, London, United Kingdom

Early stages Germ cell tumors

Surveillance or chemotherapy?

- 37 patients with stage IA female germ cell tumors
- Non dysgerminoma relapses: 8/22(36%)
- Dysgerminoma relapses: 2/9 (22%)
- 10/11 patients (91%) were successfully cured with platinum-based chemotherapy
- 1 patient died: immature teratoma G3

Early stages Germ cell tumors

Surveillance or chemotherapy?

- ❑ The overall disease-specific survival was 94%
- ❑ Careful surveillance is safe
- ❑ Excellent cure rate with platinum-based chemotherapy for the 20-40% that do relapse

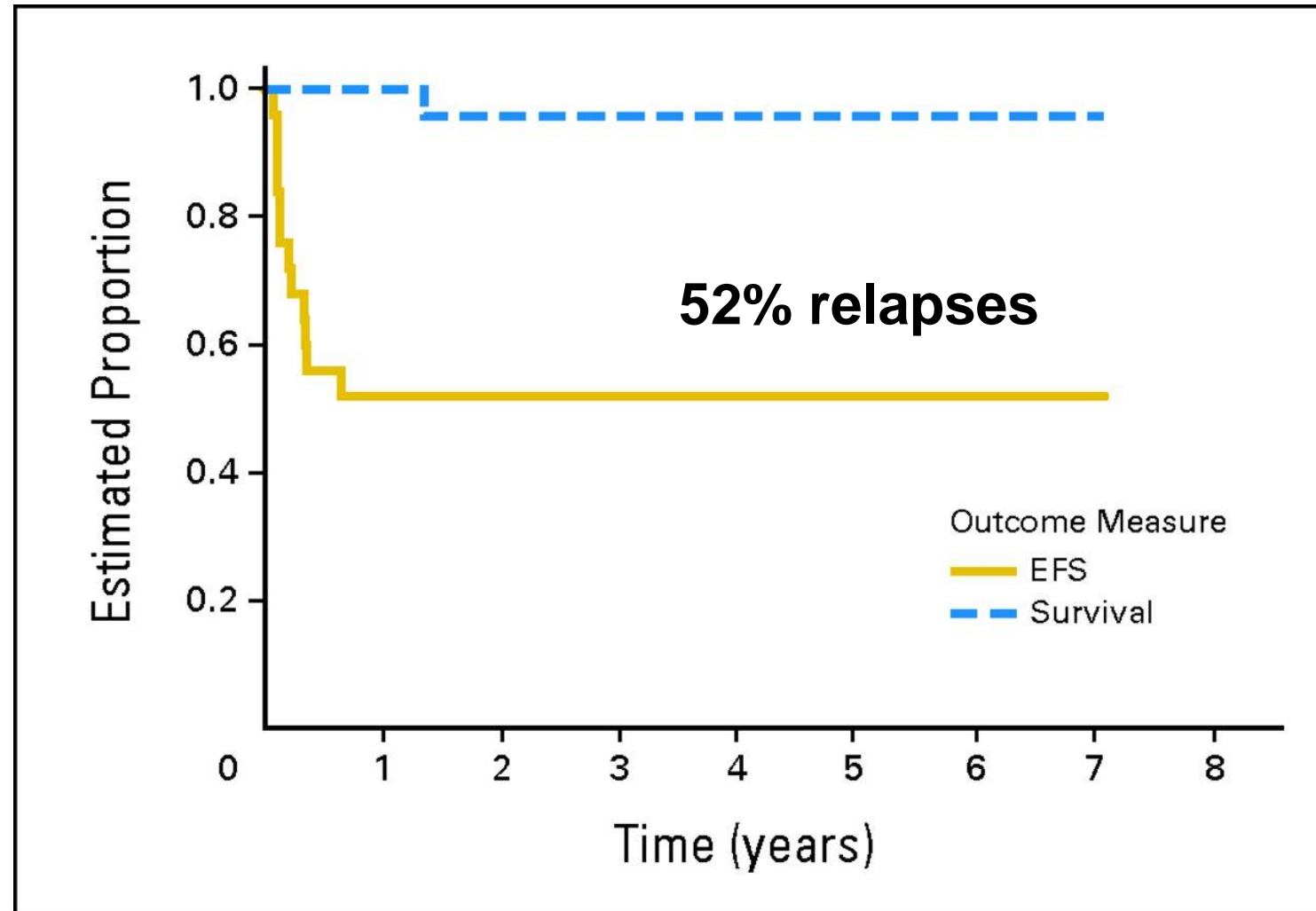
Surveillance After Initial Surgery for Pediatric and Adolescent Girls With Stage I Ovarian Germ Cell Tumors: Report From the Children's Oncology Group

Deborah F. Billmire, John W. Cullen, Frederick J. Rescorla, Mary Davis, Marc G. Schlatter, Thomas A. Olson, Marcio H. Malogolowkin, Farzana Pashankar, Doojduen Villaluna, Mark Krailo, Rachel A. Egler, Carlos Rodriguez-Galindo, and A. Lindsay Frazier

Histology	N.	%
Pure YST	8	32
YST plus MT only	3	12
YST plus IT	7	28
Mixed malignant	7	28

23/25 had elevated AFP

Event-free survival (EFS) and overall survival of pediatric and adolescent female patients with stage I ovarian germ cell tumors.



Billmire D F et al. JCO 2014;32:465-470

Rationale for surveillance

- The recurrent tumor is biologically identical to newly diagnosed cancer and treatment (BEP) is just as efficacious for recurrent tumors
 - 50%-60% of girls can be spared the potential morbidity of chemotherapy with successful outcome
-

Surveillance requirements

- ☐ Patients should be surgically staged
 - ☐ Pathology should be confirmed by a gynecologic oncology pathologist
 - ☐ Normalized markers post surgery
 - ☐ Counseling about recurrence risk
 - ☐ Reliable patient
-

Surveillance schedule

- AFP and BHCG
 - q 3 weeks through week 9
 - Every month from months 2-6
 - Every 3 months from months 6 to 24

- Radiologic imaging: frequency not mentioned

Surveillance program

Charing Cross /Mount Vernon

Time period	examination	Pelvic U/S	Tumor markers	CXR	CT chest-abdomen-pelvis
1 year	monthly	2 monthly	every 2 weeks x 6 m and then monthly x 6	2 monthly	1 M * 3 m ** 12 m
II year	2 monthly	4 monthly	2 monthly	4 monthly	
III year	3 monthly	6 monthly	3 monthly	6 monthly	
IV year	4 monthly		4 monthly	8 monthly	
Year 5-10	6 monthly		6 monthly	annually	

•If not performed pre-op

•**If clear- 2nd look laparoscopy if inadequate staging/immature teratoma

Surveillance

- ❑ Relapses occur within 1-2 years in almost all cases
 - ❑ Salvage rate high
 - ❑ Advantages- reduced toxicity, no unnecessary treatment
 - ❑ Disadvantages- more intensive follow up (consider compliance !)
-

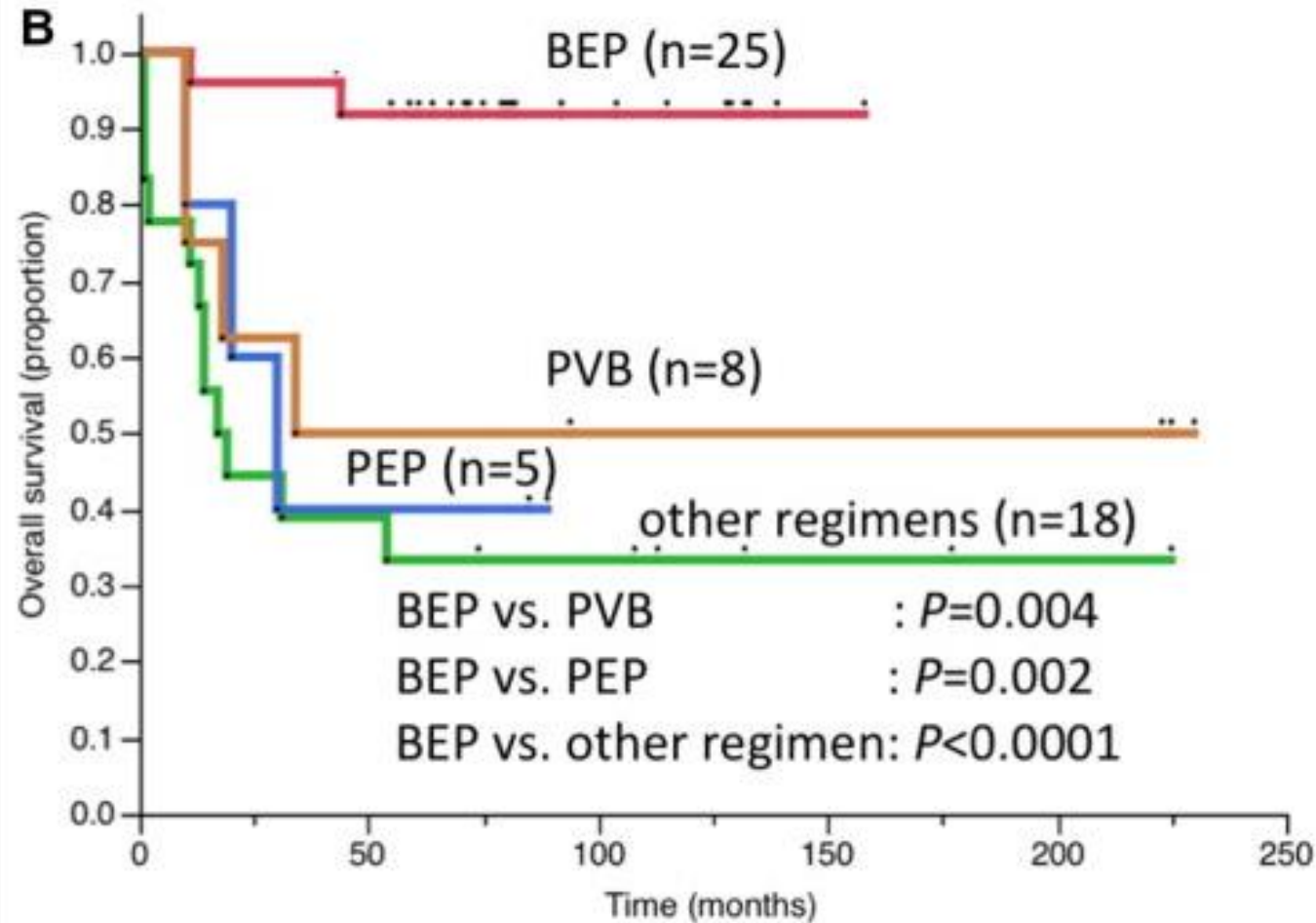
Management of advanced disease

- ❑ BEP X 4-5 represents standard of care
 - ❑ Multiple studies using various combinations and permutations do not appear superior
 - ❑ VeIP appropriate if compromised lung function
 - ❑ High dose therapy not demonstrated to be superior first line treatment
-

How important is Bleomycin

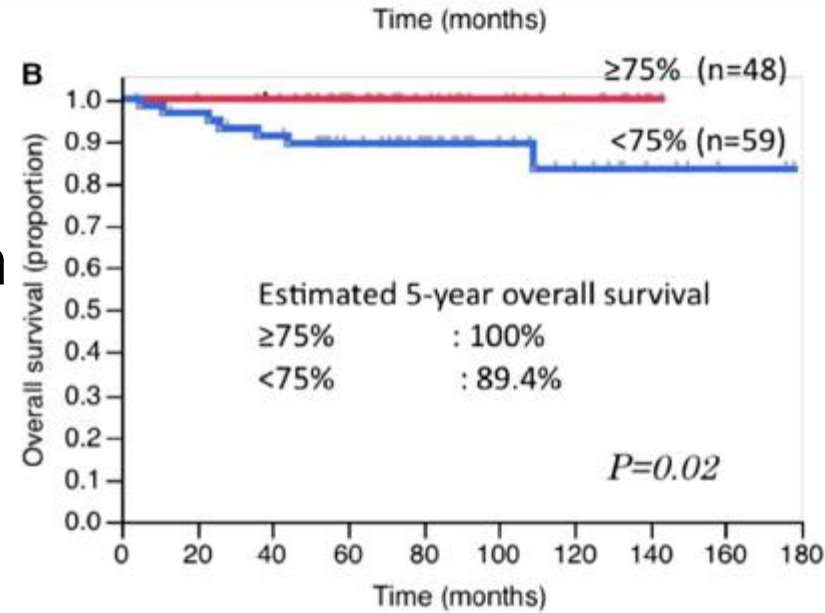
- ❑ Bleomycin should only be omitted if contraindications when 4 cycles of EP can be used
 - ❑ Inconsistent findings from trials of 4 EP vs 3 BEP
-

Survival in Stage III-IV with residual tumor according to regimen

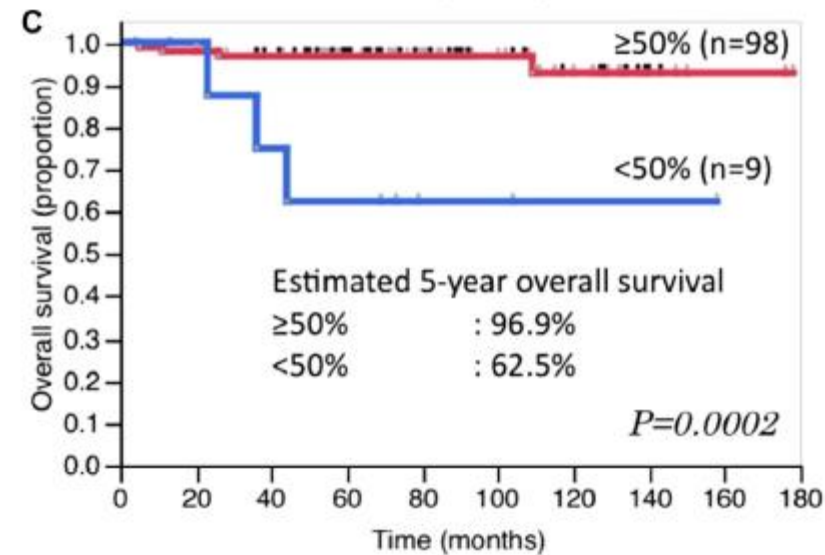


Survival according to BEP dose

Bleomycin



Etoposide



Fertility after BEP

- 16/23 patients (70%) who attempted conception gave birth to 21 healthy children

Relapse

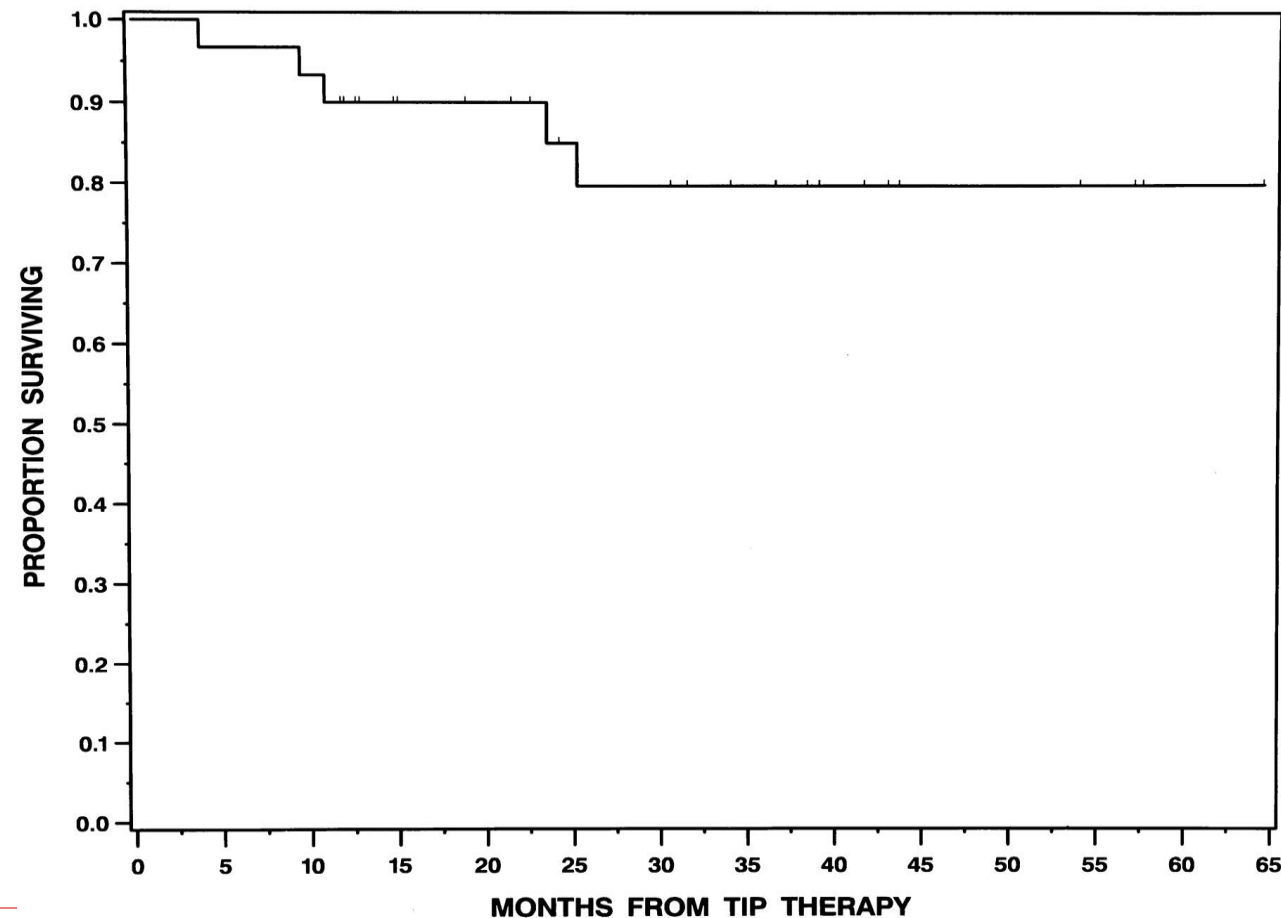
- Recurrences tend to be within 24 months
 - BEP post surveillance
 - For BEP failure:
 - Surgery
 - Chemotherapy: TIP: cisplatin, paclitaxel, ifosfamide
VIP: vinblastine (or VP16), ifosfamide, cisplatin
Gemcitabine, paclitaxel
Oxaliplatin/gemcitabine
 - Consider high dose chemotherapy with stem cell support
-

Salvage therapy TIP

Journal of Clinical Oncology 18; 2000: 2413-2418

- ❑ Treatment consisted of four cycles of TIP given 21 days apart.
 - ❑ Paclitaxel 250/m² by 24-hour infusion on day 1, followed by an ifosfamide 1.2 g/m² infusion given over 4 hours, and cisplatin 20 mg/m² on days 2 through 6.
 - ❑ 80% of 30 achieved a favorable response.
 - ❑ 22 (73%) of the favorable responses remain durable at a median follow-up duration of 33 months
-

Survival for patients with relapsed testicular GCTs treated with TIP therapy (n = 30; 25 alive)



Motzer, R. J. et al. J Clin Oncol; 18:2413-2418 2000

Stem Cell Transplant ?

European Bone Marrow Transplant Group- Randomized 280 relapsed patients to VIP/VeIP X4 vs VIP/VeIP X3 followed by High Dose Chemo and stem cell support

No advantage to High dose and stem cell support
53% 3 year survival in both arms

Stem Cell Transplant

- ❑ Results of 2 randomized trials EORTC and an intergroup study **do not** support role in first line therapy for high risk disease
 - ❑ Still contentious for salvage therapy
-

SECONDARY SURGERY

Second look laparotomy is not necessary ... however, in teratomas, residual immature teratoma or retro-conversion to mature teratoma post-chemotherapy is possible. Residual mature teratoma should be resected as they may produce “growing teratoma syndrome” with obstructive features.

CASE REPORT

-01.1999: us diagnosis of left adnexal mass (20 cm); CA125= 61.7 U/ml - α FP= 179 ng/ml

-01.1999: left salpingo-oophorectomy. Pathology: mature teratoma

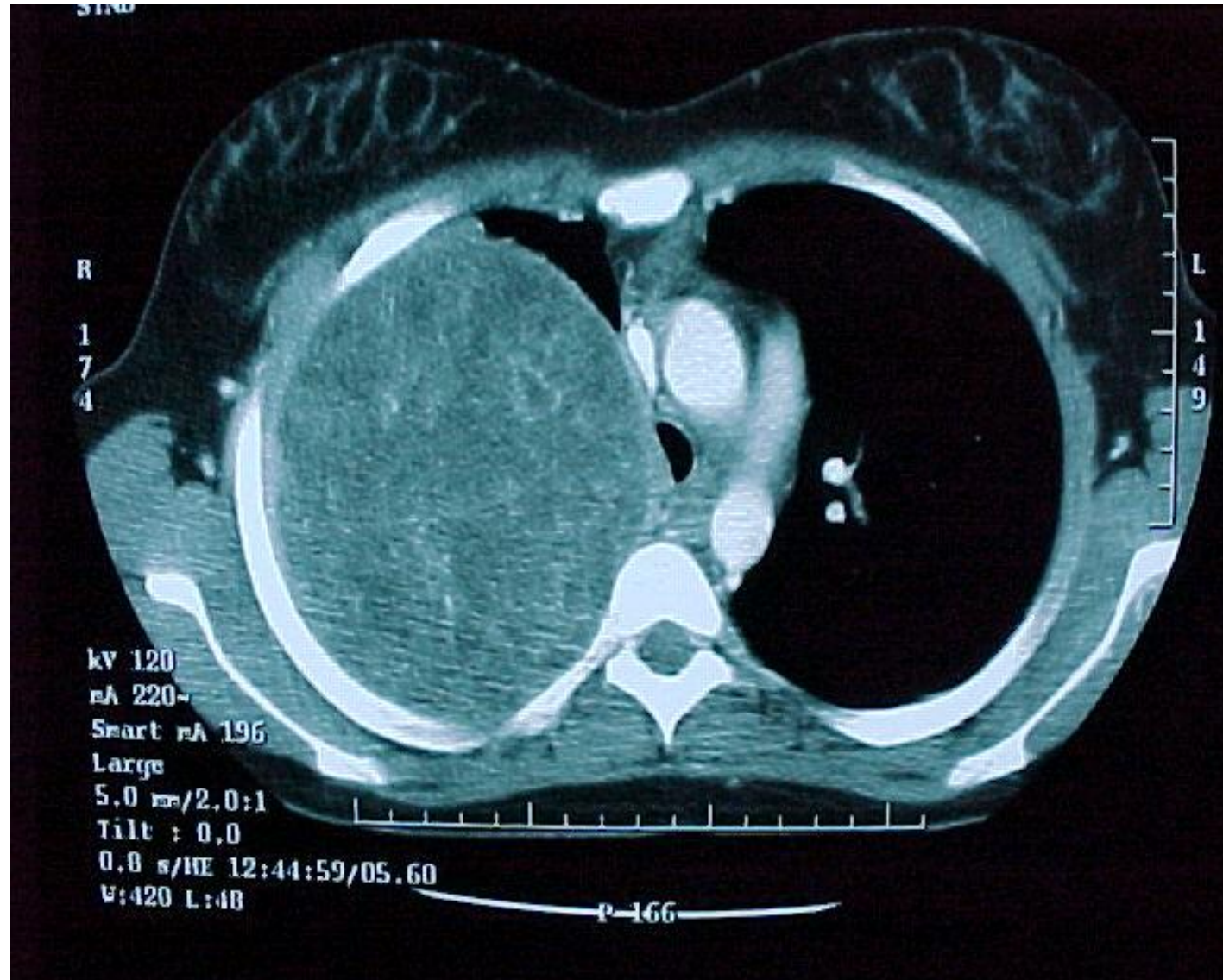
-06.2000 admission to IEO due to respiratory distress. Total body CT-scan: right lung metastasis with superior vena cava and tracheal compression + abdominal mass (5x3cm)

CASE REPORT

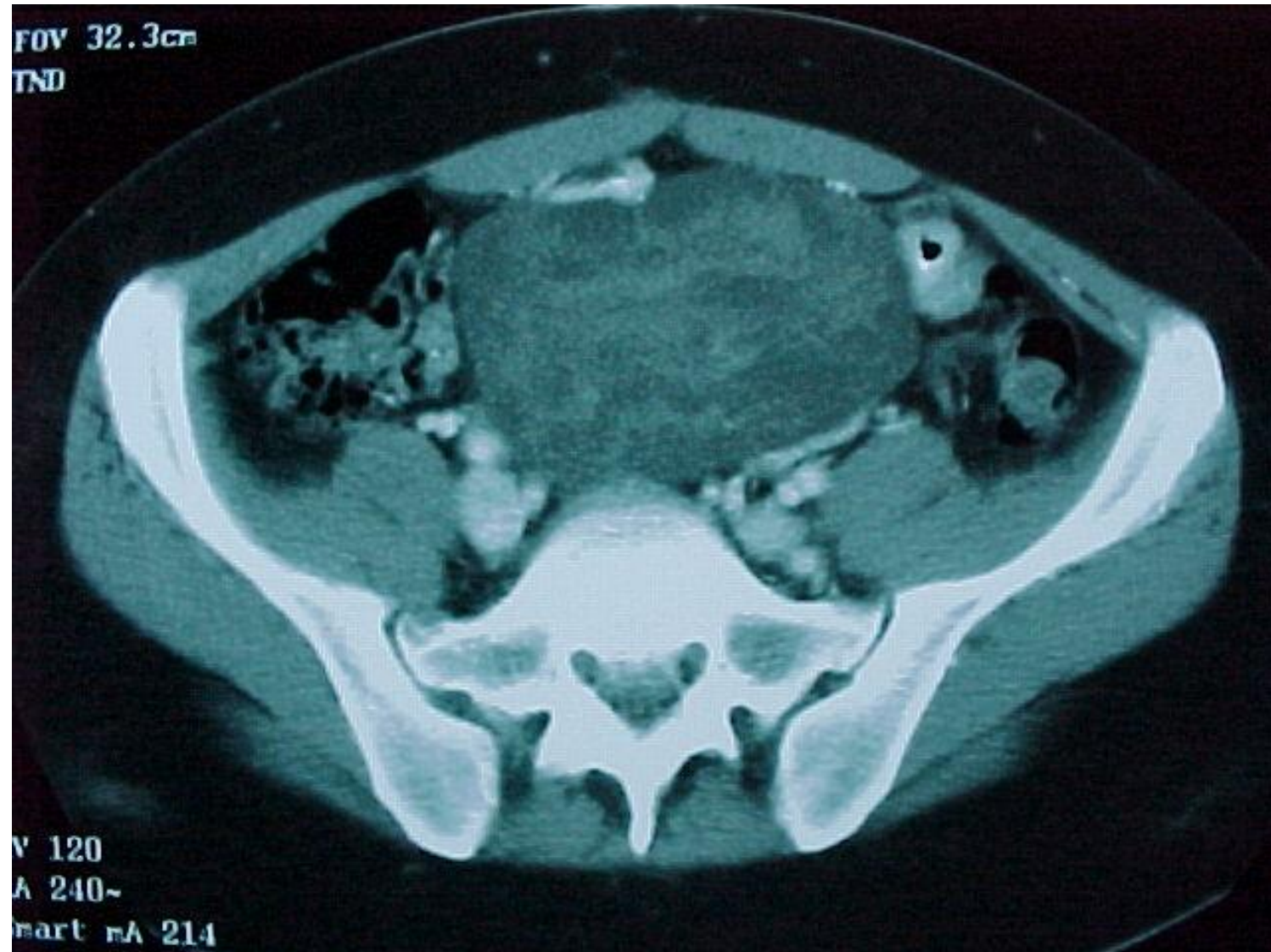
-06.2000: pathology review with diagnosis of mixed germ cell tumor (immature teratoma & yolk sac tumor)

-24.06.2000 - 12.08.2000: BEP x 3 cycles. AFP levels after chemotherapy were 147.7 ng/ml & CT scan showed progression of disease

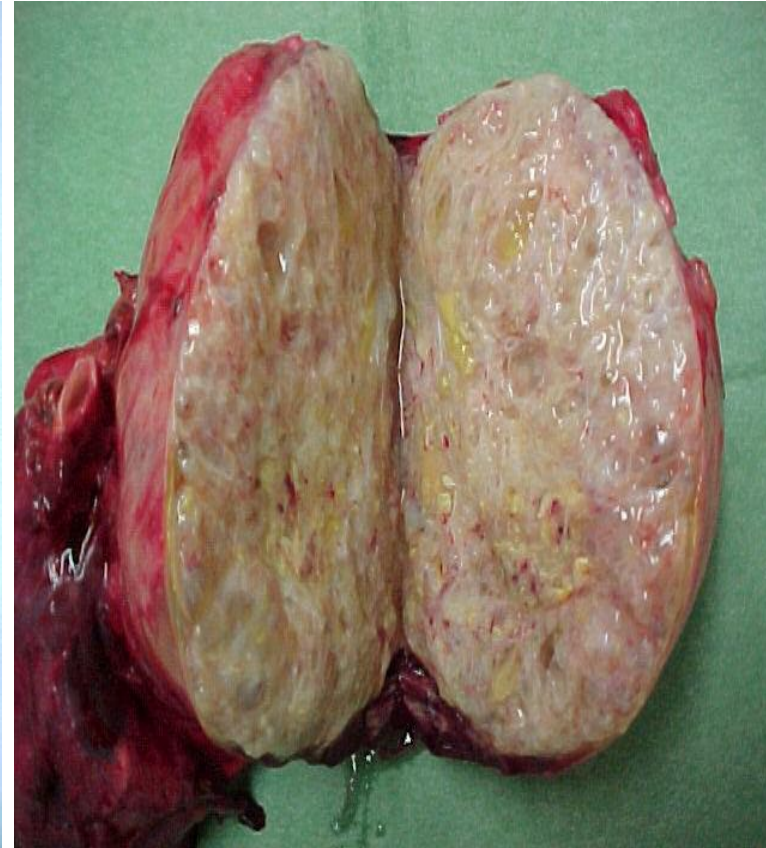
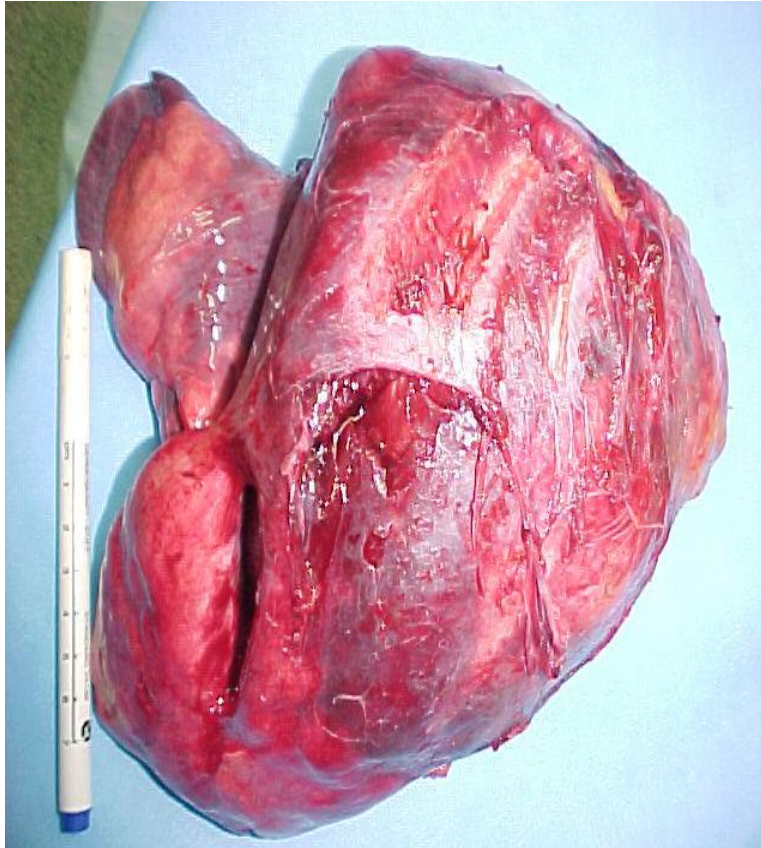
CHEST CT-scan



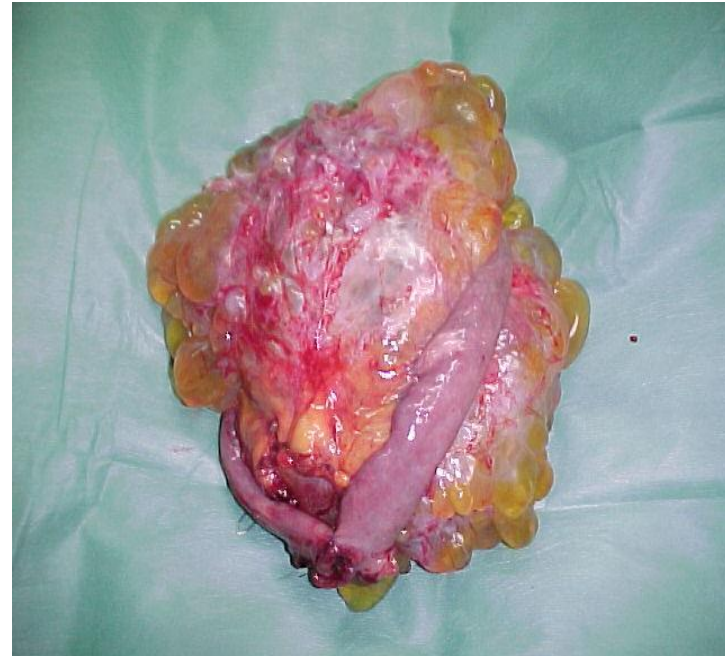
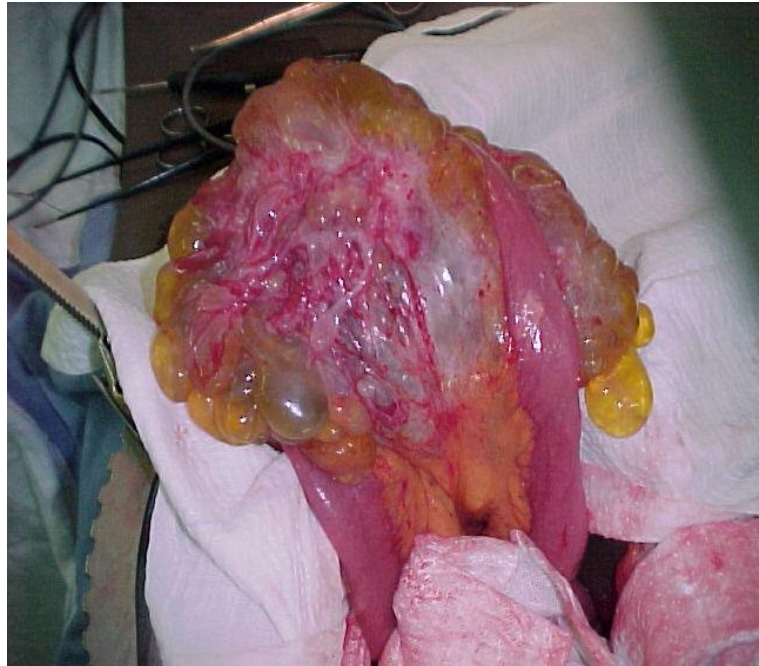
ABDOMINAL CT-scan



15.09.2000: severe respiratory distress. Right pneumectomy on emergency. Pathology: mature teratoma. Negative α FP after surgery.



31.10.2000: Abdominal tumorectomy with ileum resection and L-L anastomosis & omentectomy. Pathology: mature teratoma. 4th cycle of CT after surgery.



Long term complications

- ❑ Acute leukemia:
 - BEP in testis associated with 0,9% risk of leukemia (11q23 changes)
 - Case report of AML in ovarian GCT treated with BEP
 - Recent study showed excess leukemia risk 0,23% by 30 years after testis treatment , higher in patients receiving chemotherapy versus RT
 - ❑ Cardiovascular disease
-

Conclusions

- ✓ Paradigm of a curable malignancy
 - ✓ Good evidence base for treatment
 - ✓ Focus on reduction of toxicity in low risk and improving outcomes in high risk, relapsing patients
 - ✓ Surveillance has not been standard of care in ovarian germ cell tumors but new evidences are coming
-