Neoadjuvant Chemotherapy for Malignant Ovarian Germ Cell Tumors (MOGCT)

מרכז רפואי אוניברסיטאי סורוקה
היחידה לגינקולוגיה אונקולוגית
עמית מאיר

GCT- Key points

- Rare ovarian tumors
- First 2 decades of life
- Majority are early stage at diagnosis
- Primitive GCT and immature teratoma are highly chemo and radio sensitive
- Standard treatment-
  - Early stage- staging/ fertility sparing
  - Advanced stage- cytoreduction/ fertility sparing (non radical)
  - Adjuvant chemotherapy (BEP 3-5 cycles)
  - Limited use of radiotherapy (Dysgerminoma)

But….

- 30% advanced stage at presentation
- Fertility preservation
  - Considered safe based on chemosensitivity
  - Not always possible

- NACT acceptable for advanced EOC

- Is NACT safe and effective for the treatment of ovarian GCT to preserve fertility?

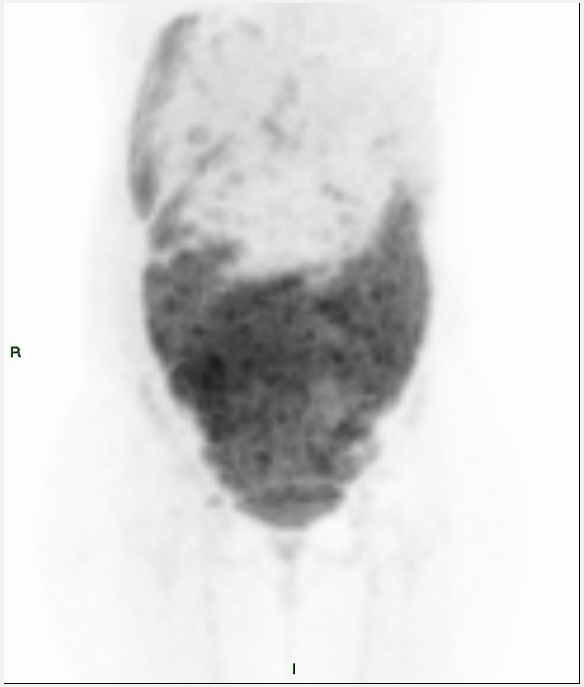
Case presentation

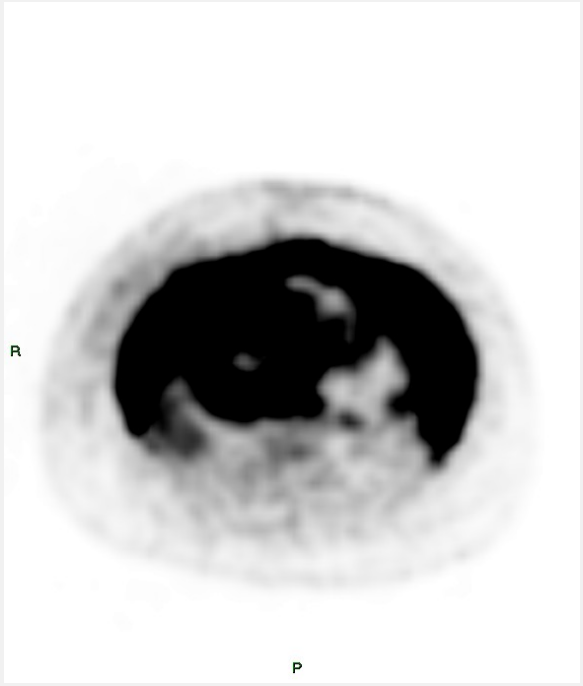
- 16 years old
- Huge plevic/ abdominal mass
- CT: huge mass, omental cake, and ascites
- Tumour markers- elevated AFP 420ng/ml
  - Normal inhibin, LDH, bHCG

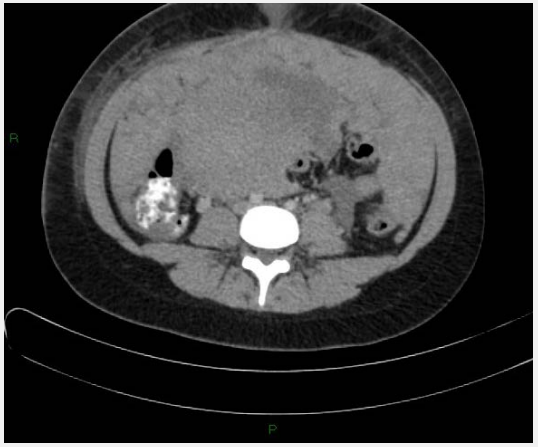
Pathology

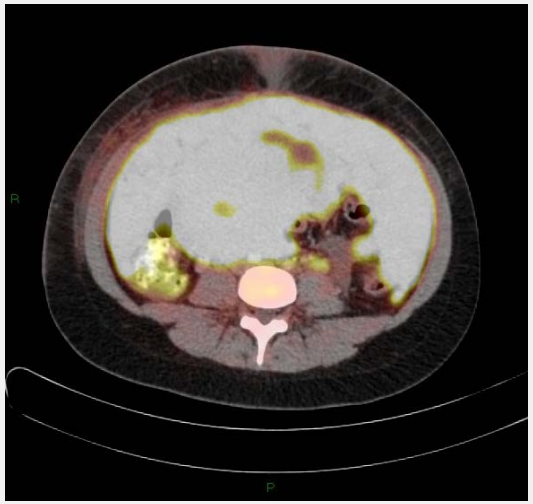
- Pelvic mass biopsy revealed – Dysgerminoma
- Immunostaining:
  - Positive for: OCT-4, CD117, Vimentin and Ki67
  - Negative for: Keratin, Calretinin, PAX8, CD3, CD20, AFP
- Ascitic cytology: Large malignant cells with high nuclear grade

PET CT









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Germ cell tumors of the ovary: Is there a role for aggressive cytoreductive surgery for nondysgerminomatous tumors?

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Article original

Tumeurs germinales malignes de l'ovaire. À propos de 36 cas

Malignant ovarian germ cell tumours: a trial of 36 cases

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Advanced germ cell malignancies of the ovary: Should neo-adjuvant chemotherapy be the first line of treatment?

A. Raveendran, S. Gupta, R. Bagga, S. C. Saha, S. Gainder, L. K. Dhaliwal, show all
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The Effect of Neoadjuvant Chemotherapy and Surgery in Children With Malignant Germ Cell Tumors of the Genital Region: A Pediatric Intergroup Trial

By Frederick Rescorla, Deborah Billmire, Charles Vinocur, Paul Colombani, Wendy London, Roger Giller, Barbara Cushing, Stephen Lauer, John Cullen, Mary Davis, and Edith Hawkins

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Neo-adjuvant chemotherapy in the treatment of advanced malignant germ cell tumors of ovary

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- 211 cases
- 23- NACT
  - Bulky disease and poor performance status
  - Received 4 cycles of BEP
  - Interval debulking
- 43 cases (standard treatment group)
  - Advanced disease

Table 1
Neo-adjuvant chemotherapy versus advanced stage (Standard Treatment Group): Base line characteristics.

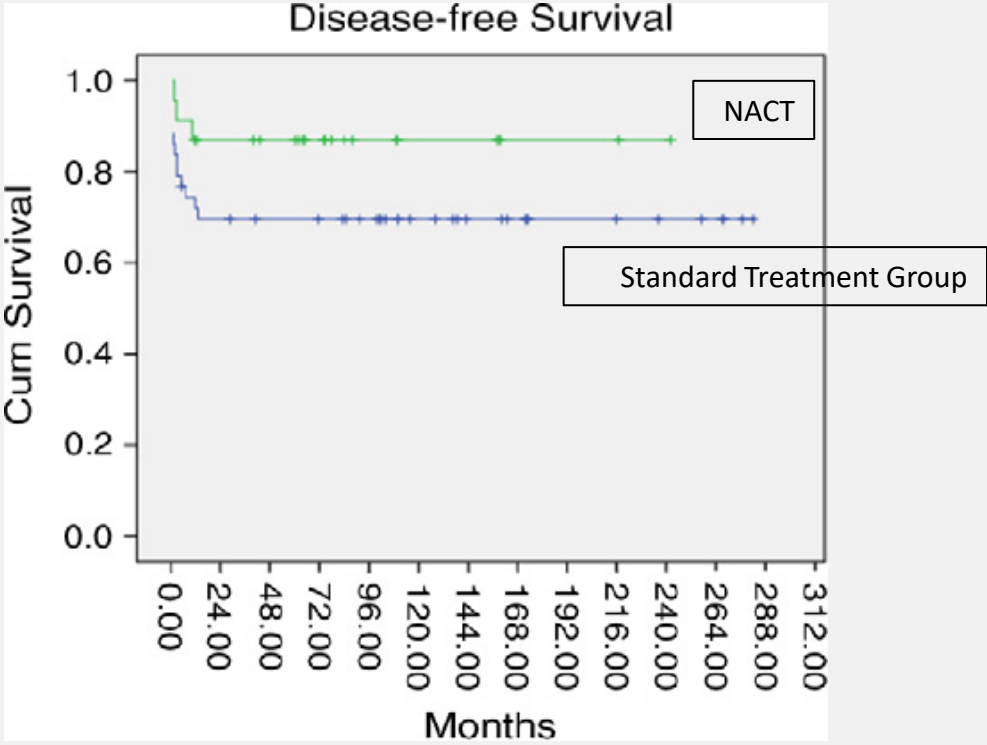
Variable	NACT (n = 23)	Advanced disease (n = 43)
Median age in years (range)	19 (14–28)	19 (6–54)
Histology	N (%)	N (%)
Dysgerminoma	14 (60.9%)	14 (32.6%)
Endodermal sinus tumor	3 (13.0%)	14 (32.6%)
Immature teratoma	0	06 (14.0%)
Mixed germ cell tumor	6 (26.1%)	08 (18.6%)
Choriocarcinoma	0	1 (2.3%)
FIGO stage		
III	20 (87%)	37 (86.0%)
IV	03 (13%)	06 (14.0%)
Median duration of symptoms (range)	2.5 months (3 days to 12 months)	4.0 (12 days to 36 months)
ECOG performance status		
1	–	29 (67.4%)
2	13 (56.5%)	13 (30.2%)
3	10 (43.5%)	1 (2.3%)
Presentation		
Abdomen distension	9 (39.1%)	27 (62.8%)
Pain in abdomen	12 (52.2%)	31 (72.1%)
Palpable lump in abdomen	18 (78.3%)	34 (80.0%)
Acute abdomen	0	1 (2.3%)
Menstrual symptoms	4 (17.4%)	4 (9.3%)
Dyspnea	39 (13.0%)	4 (9.3%)
Fever	6 (26.1%)	10 (23.3%)
Urinary symptoms	2 (8.7%)	1 (2.3%)
Ascites	4 (17.4%)	9 (20.9%)
Elevated Tumor markers		
Serum LDH	18/20	15/17
Serum AFP	10/23	17/38
Serum b–HCG	11/23	14/37
Residual disease		
	Post IDS (n = 21)	
Nil	13 (60.2%)	02 (4.7%)
1–2 cm	5 (20.4%)	7 (16.3%)
>2 cm to ≤5 cm	3 (14.2%)	4 (9.3%)
>5 cm	–	30 (69.8%)
Fertility sparing surgery	–	30 (69.8%)
Chemotherapy regimen		
BEP	23 (100.0%)	32 (74.4%)
VIP	–	01 (2.3%)
PVB	–	10 (23.3%)

Neo-adjuvant chemotherapy in the treatment of advanced malignant germ cell tumors of ovary

Table 2
Results: Neo-adjuvant chemotherapy versus Standard Treatment Group.

	Neo-adjuvant chemotherapy (n = 23)	Standard Treatment Group: (n = 43)
Response to chemotherapy		
CR	16 (70.0%)	26 (60.5%)
PR	05	07 (16.3%)
CR + PR	21 (91.3%)	33 (76.8%)
Progressive disease	1	2 (4.7%)
Lost to follow-up/NE	1	6 (14.0%)
Died of chemo-toxicity	0	2 (4.7%)
CR + PR according to subtype		
Dysgerminoma	12/14 (85.7%)	11/14 (78.6%)
Nondysgerminoma	9/9 (100.0%)	16/29 (76%)
Median follow-up in months (range)	74 (40 to 242 months)	101 (41 to 282 months)
Current status		
Alive	21 (91.3%)	30 (70%)
Died	2	13
Reproductive functions		
Eligible patients	21	30
Menstruation: Yes	18 (85.7%)	17 (56.6%)
Surgical menopause	0	11*
Married and conceived (Pregnancies)	10/10 (13)	12/12 (16)
Unmarried	08	04
Unknown	03	01
Mean disease-free survival	230.96 months (95% CI 209.8 to 252.1)	209.2 months (95% CI 172.03 to 246.3)

CR- complete response, PR-partial response, NE: not evaluable,
* One patient had dysgenetic gonad and another had primary amenorrhea.



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Role of neoadjuvant chemotherapy in the management of advanced ovarian yolk sac tumor

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- 127 cases
- 63% stage III/IV
- 21NACT (BEP 1-3, ID, consolidation RX)
  - Bulky disease
  - Massive ascites
  - Fixed tumor
  - Comorbidities/ poor performance status
- 32 PDS, ACT

Role of neoadjuvant chemotherapy in the management of advanced ovarian yolk sac tumor

Table 1
Comparison of patients profile between the NACT and PDS groups.

Variables	NACT (N = 21)	PDS (N = 32)	*P* value
Mean age (years)	23	25	0.313
Ovarian tumor size			
>20 cm	16 (76%)	4 (12%)	<0.001
≤20 cm	5 (24%)	28 (88%)	
AFP level			
$>3.5 \times 10^4$ ng/mL	10 (48%)	4 (12%)	0.005
$\leq 3.5 \times 10^4$ ng/mL	11 (52%)	28 (88%)	
Pleural effusion			
Present	9 (43%)	9 (28%)	0.268
Absent	12 (57%)	23 (72%)	
Ascites			
>100 mL	20 (95%)	24 (75%)	0.071
≤100 mL	1 (5%)	8 (25%)	
Histology			
Pure OYST	14 (67%)	23 (72%)	0.686
Mixed OYST	7 (33%)	9 (28%)	
Stage			
III	13 (62%)	27 (84%)	0.063
IV	8 (38%)	5 (16%)	

Table 2
Tumor status before and after NACT (N = 21).

Variables	Before NACT	After NACT	*P* value
Mean ovarian tumor size (cm)	20.7 ± 5.7	17.0 ± 3.3	0.016
Median AFP level (ng/mL)	3.3×10^4	6.6×10^2	<0.001
Presence of pleural effusion – n (%)	9 (43)	3 (14)	0.040
Ascites >100 mL – n (%)	20 (95)	6 (29)	<0.001

Role of neoadjuvant chemotherapy in the management of advanced ovarian yolk sac tumor

- Optimal number of chemotherapy- no more than three:
  - Three cycles were enough to achieve optimal effect
  - Tumor size decrease less and less between cycles
- NACT did not increase number of overall chemotherapy cycles

Role of neoadjuvant chemotherapy in the management of advanced ovarian yolk sac tumor

Table 3
Peri-operative parameters and post-operative complications between the NACT and PDS groups.

Parameter	NACT (N = 21)	PDS (N = 32)	*P* value
Blood loss (mL)	200	450	0.018
Transfusion needed — n (%)	3 (14)	8 (25)	0.494
Transfusion (unit)	3.3 ± 1.1	3.2 ± 1.0	0.910
Operation time (min)	120	130	0.121
Hospital stay (days)	11 ± 1.9	13 ± 2.7	0.062
Post-operative complications — n (%)			
Bowel obstruction	1 (4.8)	5 (16)	0.384
Urinary tract infection	3 (14)	3 (9.4)	0.671
Lung infection	0	1 (3.1)	1.000
Wound infection	2 (9.5)	1 (3.1)	0.555
Thromboembolism	1 (4.8)	0	0.396
Total	7 (33)	10 (31)	0.874

- optimal debulking <2cm equally achieved
- complete debulking
  - NACT 80%
  - PDS 44%

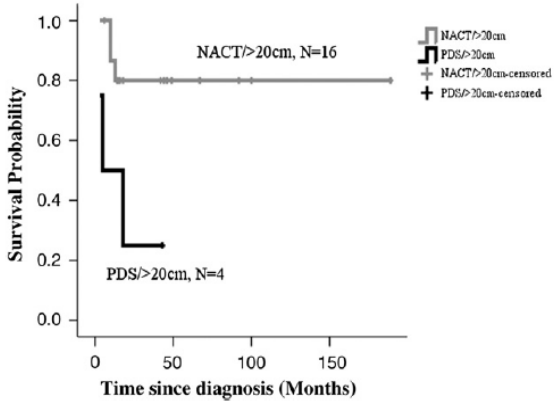
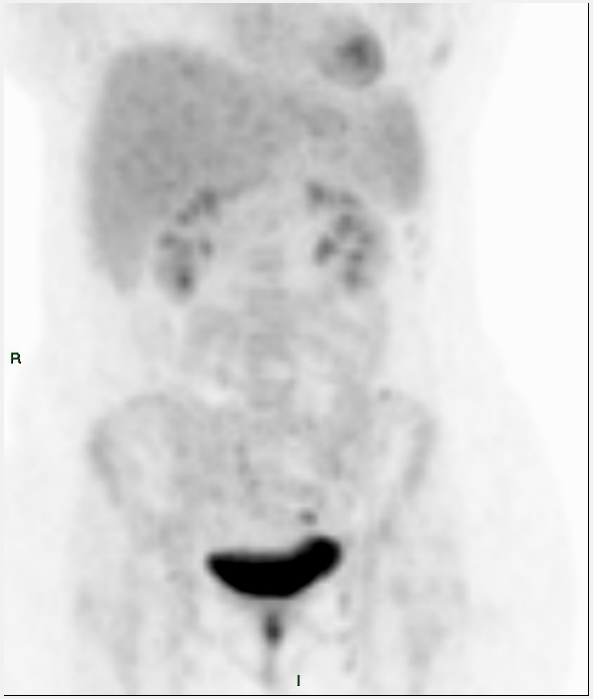
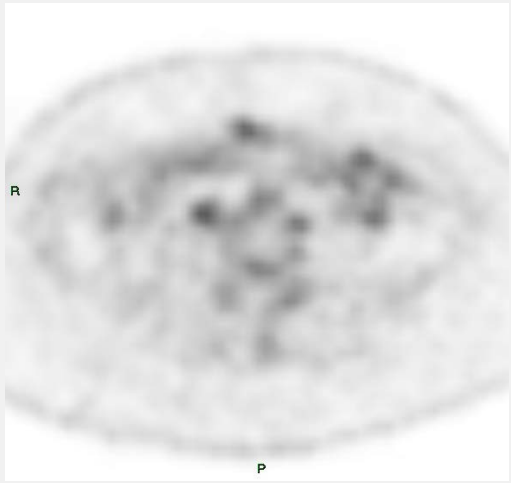


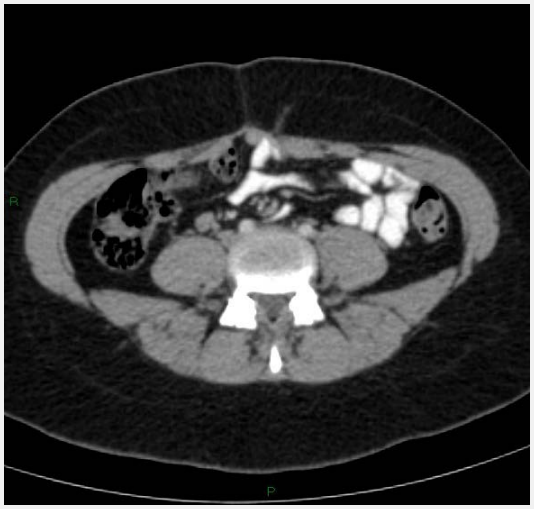
Fig. 3. Kaplan–Meier curves of progression free survival in patients with ovarian tumor size >20 cm. Gray line: NACT group. Black line: PDS group.

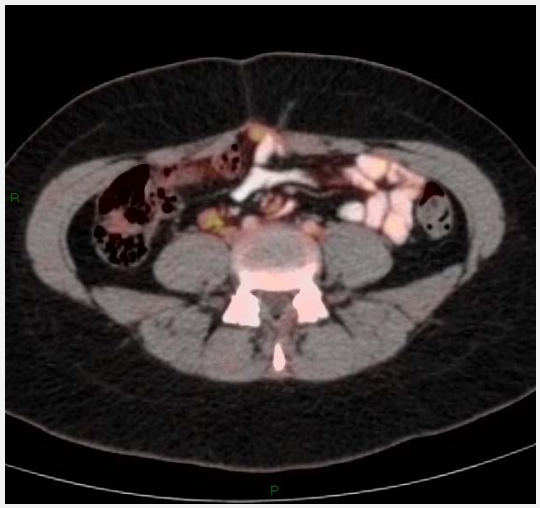
After 2 cycles of BEP

- Complete response
  - AFP- reached normal levels
  - On PET CT:









Case presentation

- Fertility sparing operation:
  - Right salpingo-oophorectomy, pelvic lymphadenectomy, omentectomy and appendicectomy
- No macroscopically residual disease
- Pathology- No residual viable tumour seen
- Received 2 additional chemotherapy
- Disease free- 2 years of followup

Conclusion

Neo-adjuvant chemotherapy may be a reasonable option in patients with extensive intra-abdominal disease

- When initial debulking surgery is not an option
- Where general condition is poor
- When increased risk of surgical morbidity
- When condition precludes fertility sparing surgery

Questions

- Should we operate on CR patients?
- Is adjuvant treatment needed for pathological CR?
- Different types of chemotherapy?
- Chemo effects on remaining ovary?
- Is it also applicable for SCST?
- Is it also applicable for non Ovarian GCT?
- Sensitivity of frozen section in the diagnosis of GCT’s