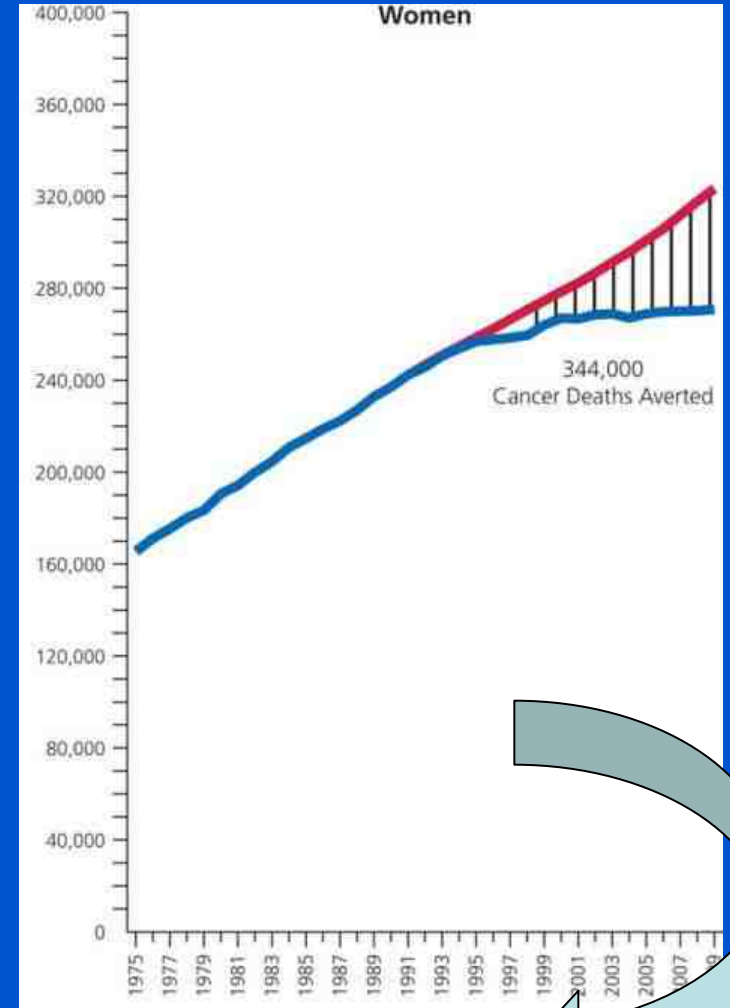
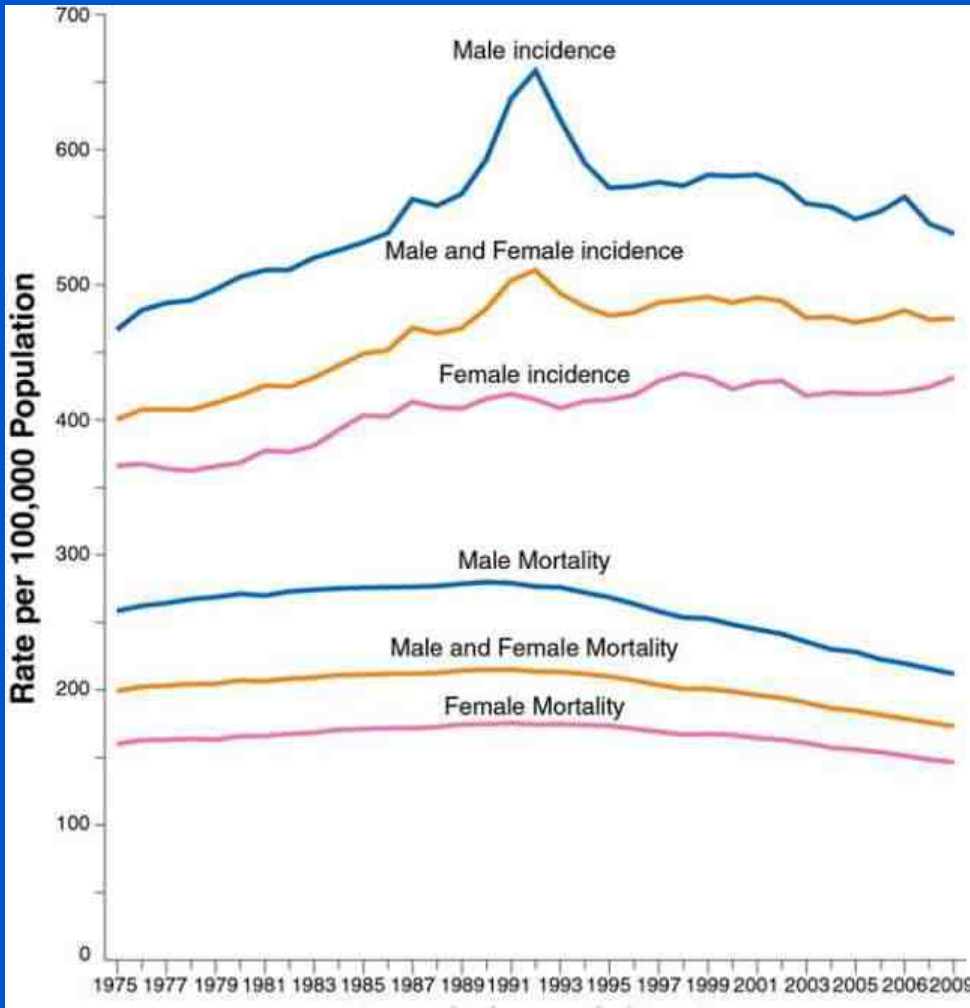




Fertilite Koruyucu Laparoskopik Cerrahi Teknikler

Murat Sönmezer
Ankara Üniversitesi Tıp Fakültesi



Kanseri ile ilgili uzun dönem komplikasyonlar

Kanser İnsidansı

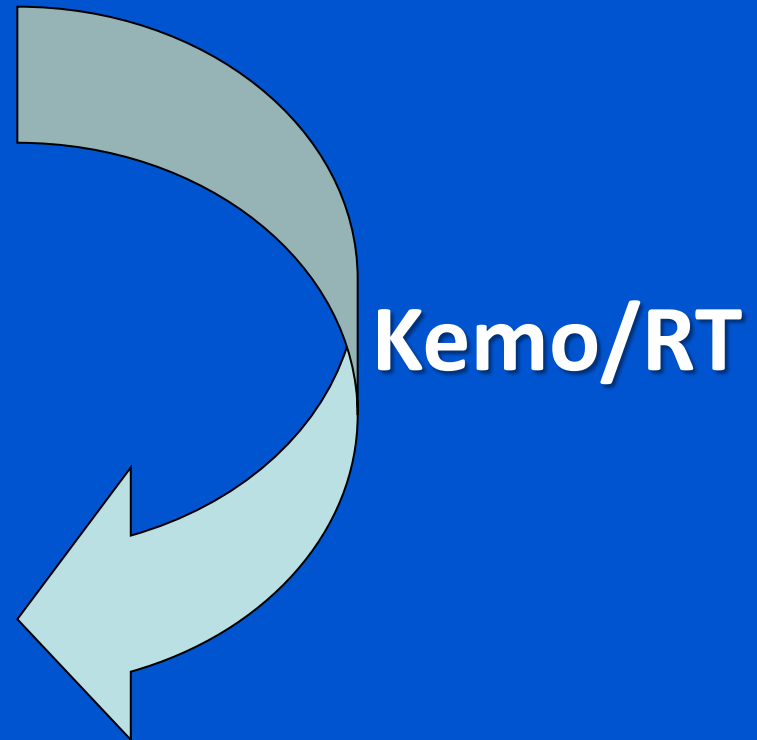
0-40 $\Rightarrow 1/50$

40-50 $\Rightarrow 1/11$

Yaşam boyu $\Rightarrow 1/3$

POF $\Rightarrow \%1 (<40)$

$\Rightarrow \%0.1 (<30)$



Fertilite Koruyucu Laparoskopik Cerrahi

1. Ovaryan doku kriyoprezervasyonu
2. Ovaryan transpozisyon
3. Ovaryan rezerv koruyucu laparoskopik cerrahi

Overyan kriyo. vs. oosit/embriyo kriyo.

Overyan kriyoprezervasyon

Oosit/embriyo kriyoprezervasyonu

Avantaj

- Kemo gecikmez
- Prepubertal tek seçenek
- Endokrin fonksiyonlar geri döner

- Teknik standart
- Yüksek başarı oranı
- Yaygın kullanım

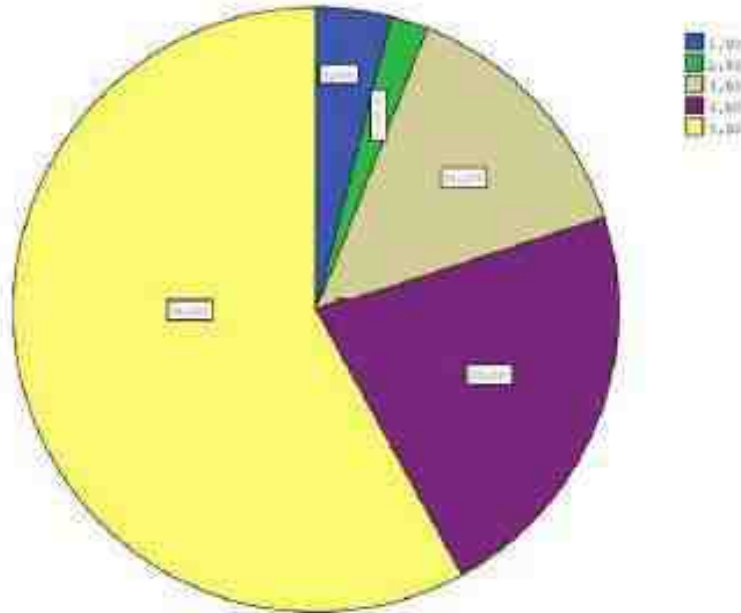
Dezavantaj

- L/S gerekli
- ~30 gebelik
- Kanseri yayılımı ?

- 2-3 hafta gerekli
- Sınırlı sayıda oosit /embriyo
- Çocuklarda kolay uygulanabilir değil

Fertilite Prezervasyonunun Yaşam Kalitesi Üzerine Etkisi

n=86



Graph 4: Motivational morale contribution of ovarian cryopreservation to patients' struggle with a malignancy. (1-5, 1; no effect, 5; maximum boosting morale)



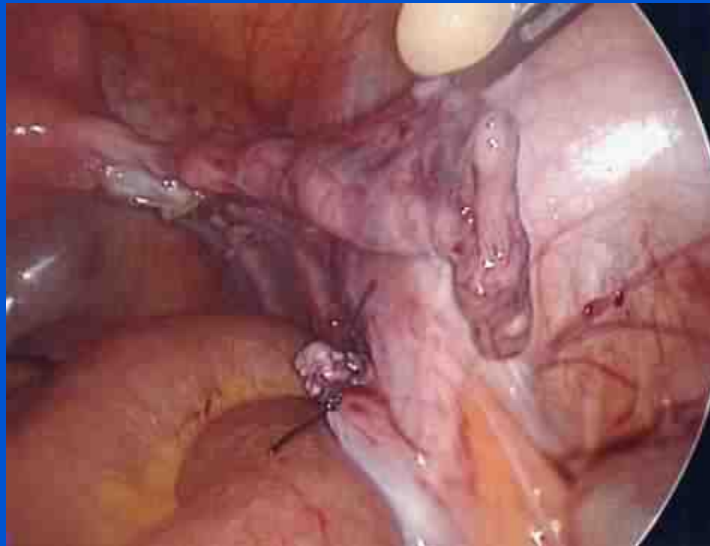
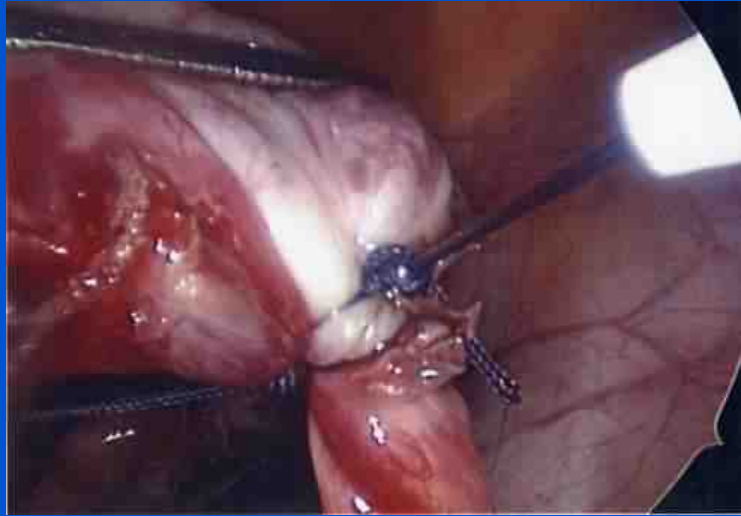
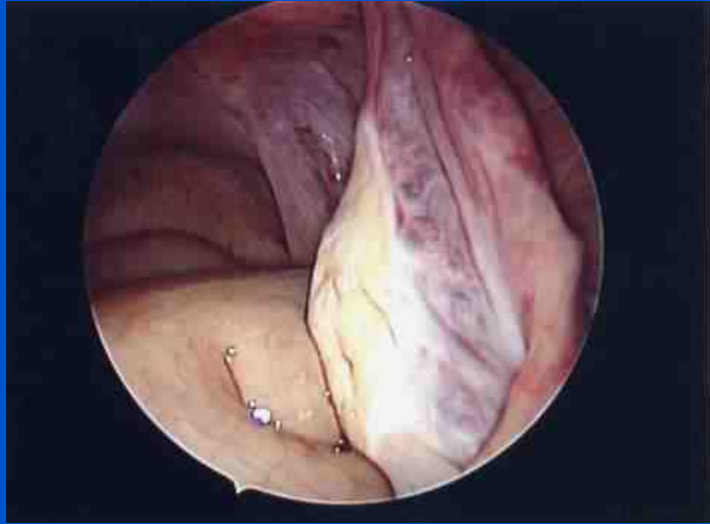
Overyan Doku Kriyoprezervasyonu ve Transplantasyonu

Neden over dokusu kriyo?

Ovaryan korteks \Rightarrow «%95 primordial foliküller»

- I. mayozda diplotenin profaz aşamasında durmuş foliküller
- Yüzey/hacim oranı yüksek
- Zona pellusida yok
- Fertilitate prezervasyonu / endokrin fonksiyonlar

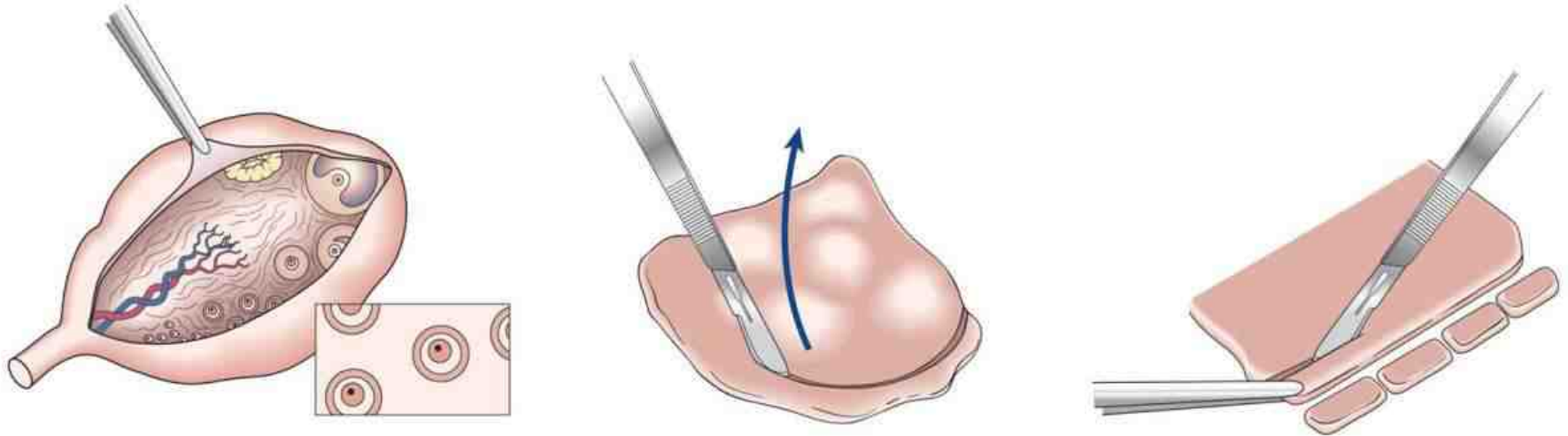
Over Dokusunun Eldesi



Laparoskopik Over Dokusunun Eldesi



Overyan Kortikal Dondurma



- 5x5x1 mm
- 3x5x1 mm

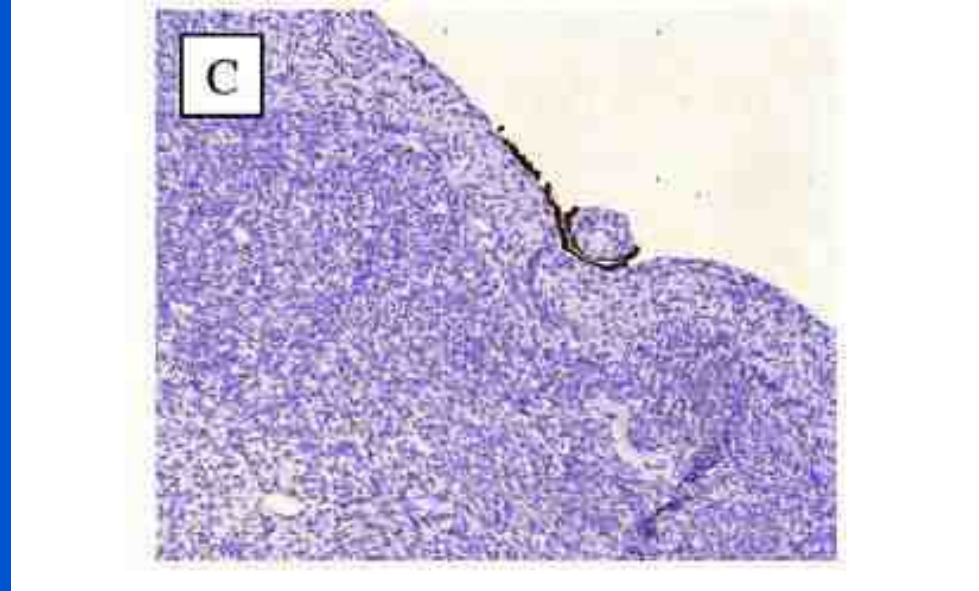
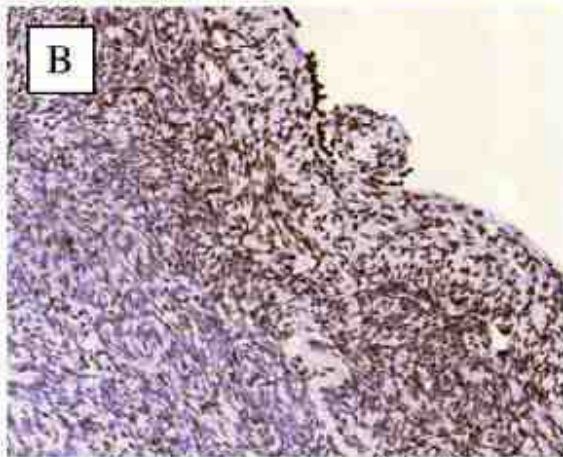
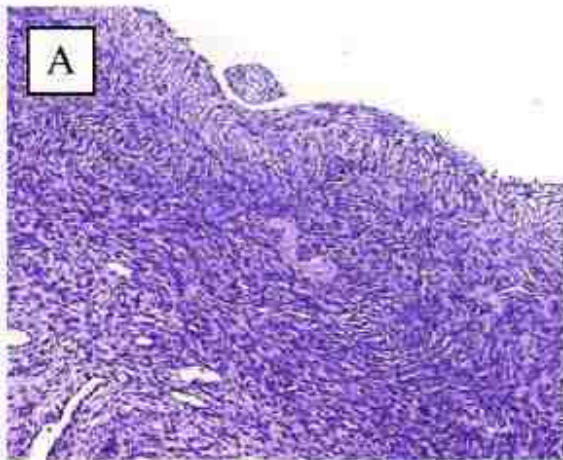
Ovaryan Metastaz Riski

Low risk of ovarian involvement	Squamous cell carcinoma of the cervix Ewing's sarcoma Breast cancer Stage I-III Infiltrative ductal Wilms' tumor Non-Hodgkin's lymphoma Hodgkin's lymphoma Osteogenic sarcoma Non-genital rhabdomyosarcoma
Moderate risk of ovarian involvement	Breast cancer Stage IV Infiltrative lobular Colon cancer (including tumors of rectum and appendix) Adeno/adenosquamous carcinoma of the cervix Upper gastrointestinal system malignancies
Cancers with high risk of ovarian involvement	Leukemia Burkitt lymphoma Neuroblastoma Genital rhabdomyosarcoma

*Sonmezer&Oktay
Cell and Tissue Res, 2005*

Erken Evre Meme Kanseri Overyan metastaz

Ovarian cortex from one of the 51 women with breast cancer. Histologic and immunohistochemical analysis shows no signs of metastatic infiltration. (A) H&E. (B) WT-1. (C) CK-7. Magnification, $\times 10$.



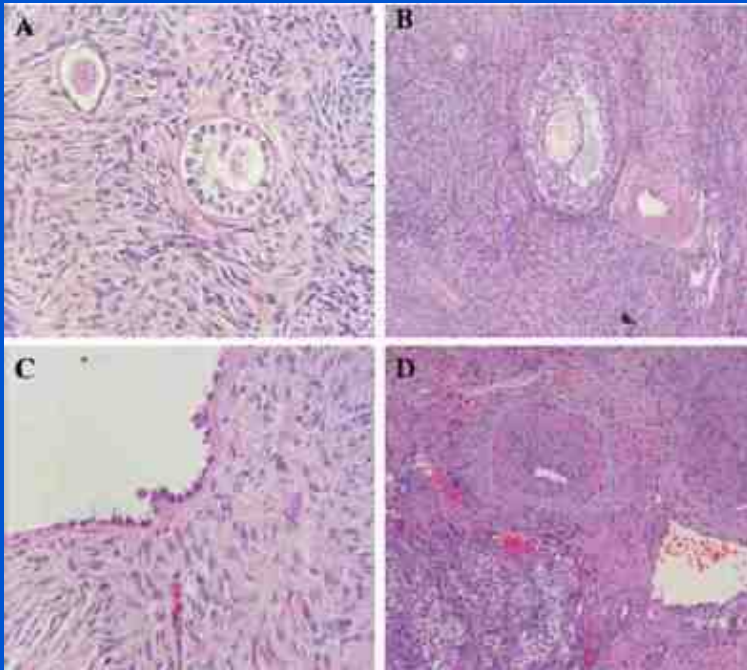
Ovaryan metastaz : 0/51

Rosendahl, Fertil Steril, 2011

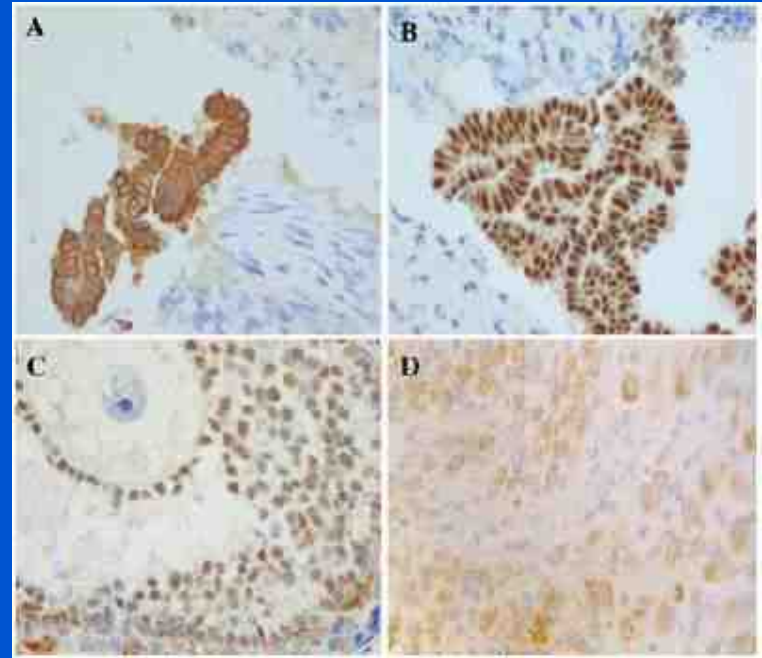
Erken Evre Meme Kanseri

Overyan metastaz (histoloji ve IHC)

IHC



Standart histoloji



Overyan tutulum: overyan kriyo yapılan hastalar 0/63 hasta (100 kortikal parça)

Hodgkin lenfoma

Overyan metastaz

- Lenfoma - 26 hasta
- Standart histoloji ve IHC ile metastaz gösterilememiş

Lösemi / ovaryan metastaz

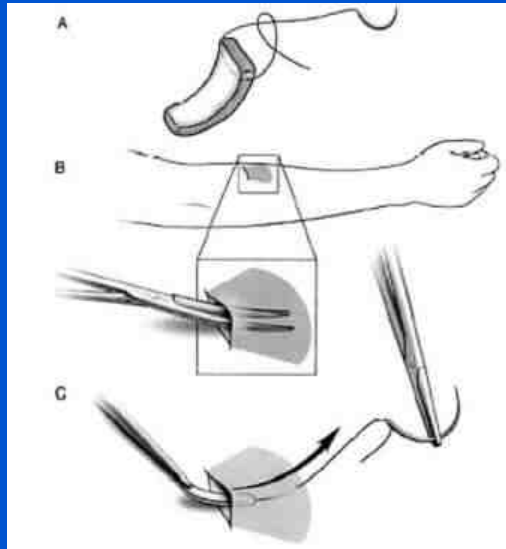
Patient no.	Age at OTC, y	Pathology	Gonadotoxic chemotherapy before OTC*	Molecular markers	Ovarian tissue PCR	Macroscopic evaluation of grafts	Microscopic evaluation of grafts	Microscopic evaluation of mouse livers
1	31	CML	0	BCR-ABL	Positive	Normal	Normal	Normal
2	17	CML	0	BCR-ABL	Negative	Normal	Normal	Normal
3	30	CML	0	BCR-ABL	Positive	Normal	Normal	Normal
4	19	CML	0	BCR-ABL	Negative	Normal	Normal	Normal
5	32	CML	0	BCR-ABL	Negative	Normal	Normal	Normal
6	19	CML	0	BCR-ABL	Negative	Normal	Normal	Normal
7	15	ALL	1, 8	BCR-ABL	Positive	Normal	Normal	Normal
8	21	ALL	0	E2A-PBX1	Positive	2 leukemic ovarian masses	Leukemic invasion	Normal
9	27	ALL	(2, 3, 4, 5, 6) ×2	Ig and TCR-γ	Negative	Normal	Normal	Normal
10	20	ALL	1, 2, 3, 4, 7, 8	Ig and TCR-γ	Positive	Normal	Normal	Normal
11	12	ALL	0	Ig	Positive	Normal	Normal	Normal
12	15	ALL	1, 2	None	NA	Diffuse leukemic masses	Leukemic invasion	Positive
13	15	ALL	0	Ig	Positive	1 leukemic ovarian mass	Leukemic invasion	Normal
14	14	ALL	0	Ig	Positive	Diffuse leukemic masses	Leukemic invasion	Positive
15	16	ALL	1, 2	Ig	Negative	Normal	Normal	Normal
16	5	ALL	1, 2	Ig and TCR-γ	Negative	Normal	Normal	Normal
17	3	ALL	1, 2	None	NA	Normal	Normal	Normal
18	11	ALL	1, 2	TCR-γ	Positive	Normal	Leukemic invasion	Normal

Transplantasyon Teknikleri

Orthotopik



Heterotopik



Xenograft



Nevaskülarizasyon İskemisi

İskemi hasarı azaltılabilir mi?

- Antiapoptotik ajan kullanımı «S1P»
- Overyan fragmanların plazmadan zengin platelet ile muamele edilmesi
- Kriyoprezervasyon öncesi 5°C'de 24 saat overyan fragmanların bekletilmesi
- VEGF/aspirin kullanılması

Soleimani , PlusOne , 2011
Callejo, J Ovarian Res, 2013
Isachenko , Clin Lab, 2012

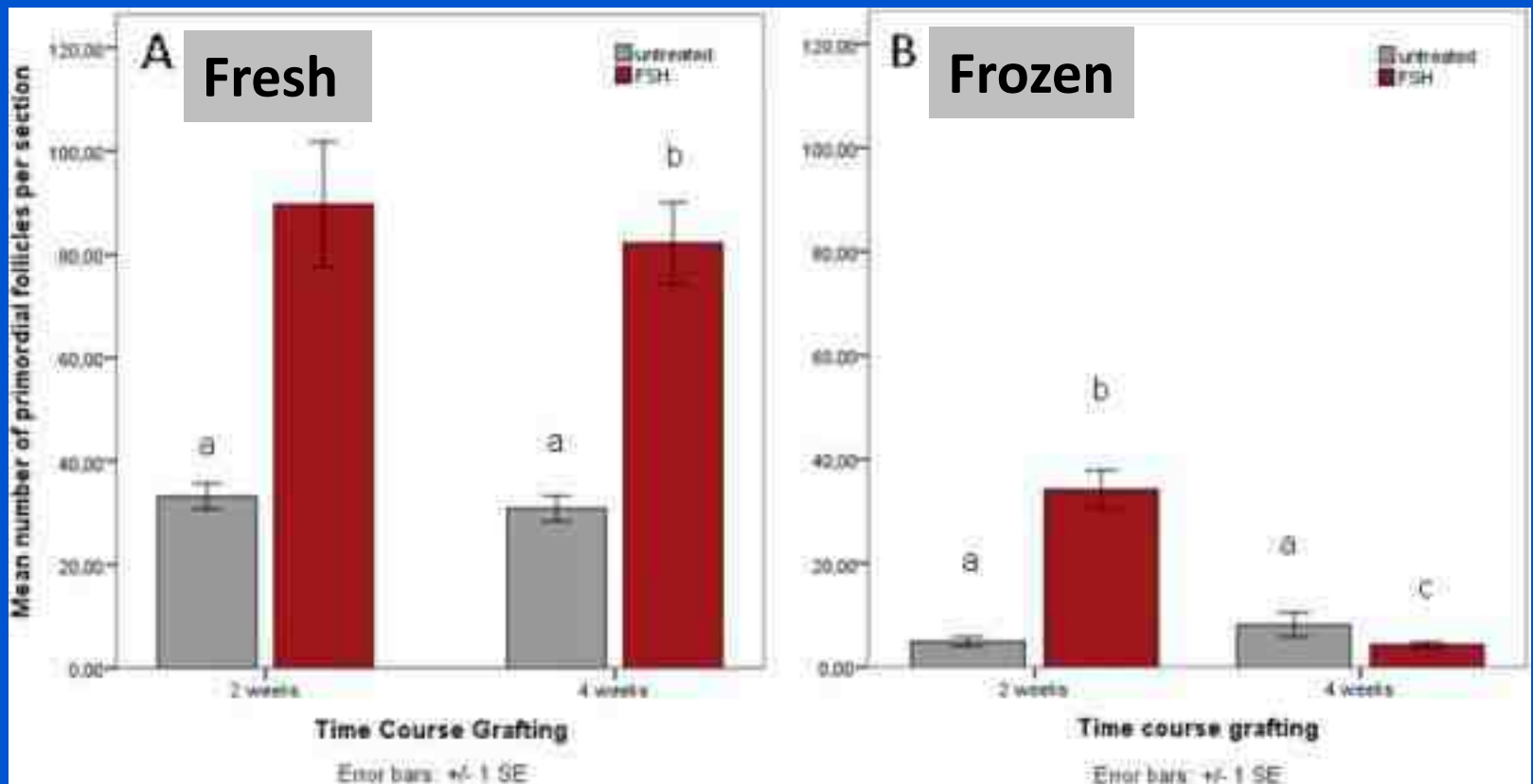
Transplantasyon Sırasında GnRH-a/FSH Kullanımı

- «GnRH-a» \Rightarrow belirgin folikül kaybı
- Ooforektomi \Rightarrow Artmış folikül sağkalımı
- Kısa dönem gonadotropin kullanımı

Oktay Fertil Steril, 2000

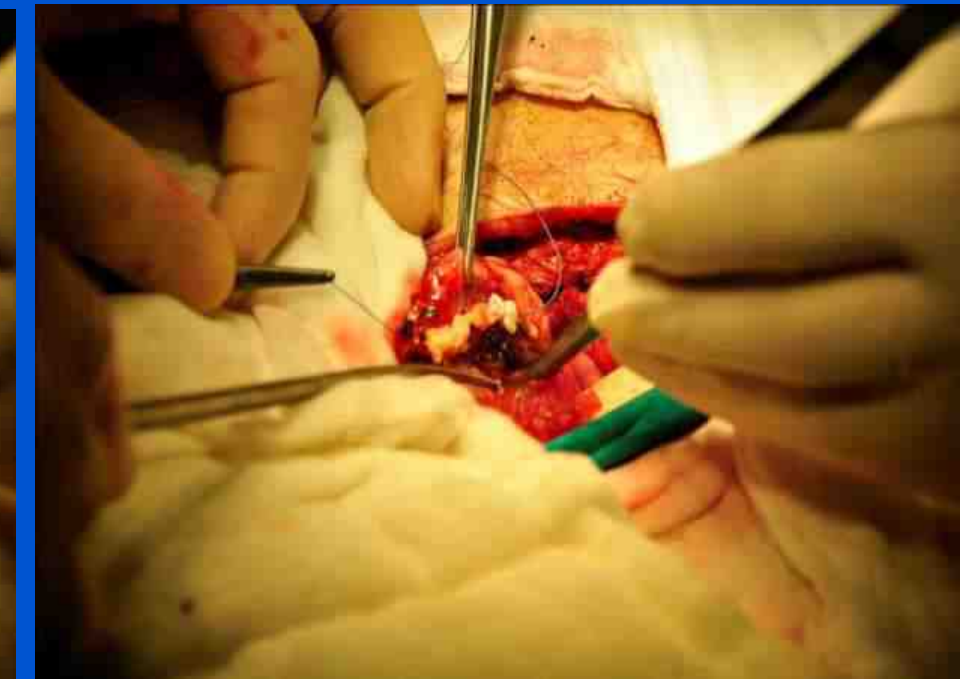
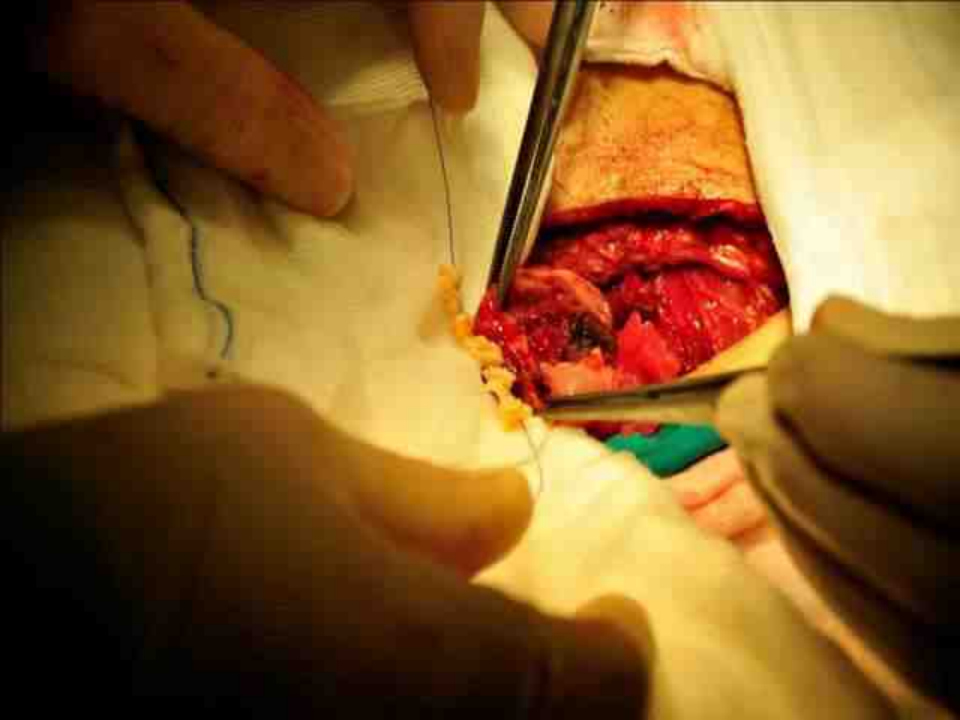
Maltaris, Reproduction, 2007 ;Maltaris, Fertil Steril, 2007

Transplantasyon Sirasinda FSH Kullanimi



Overyan Dokunun Hazırlanması

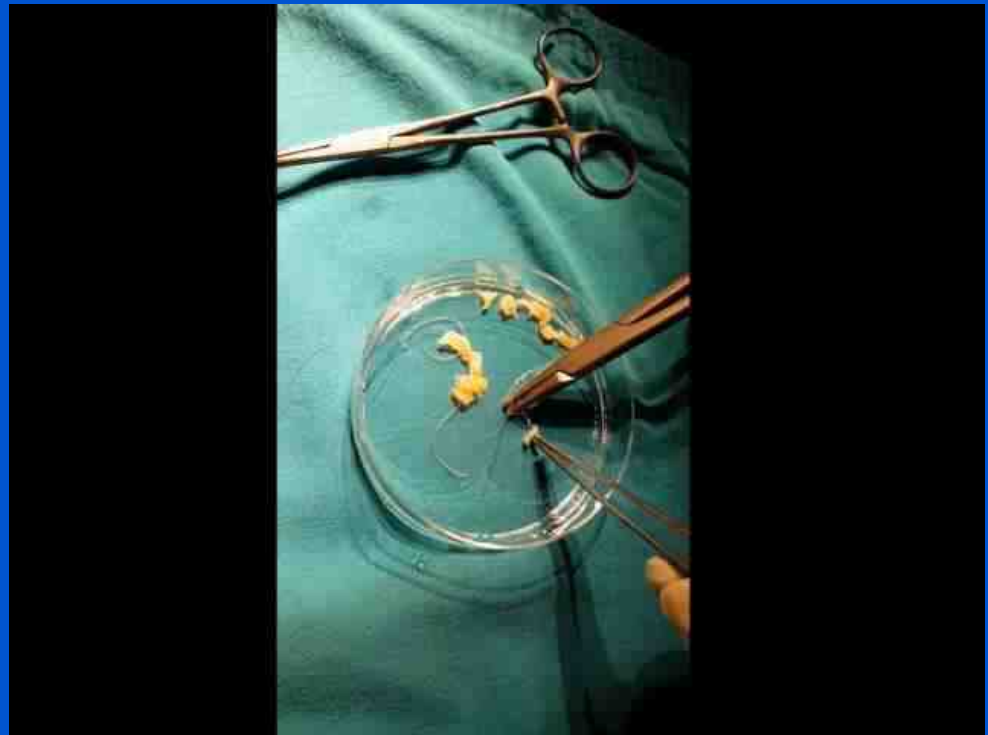
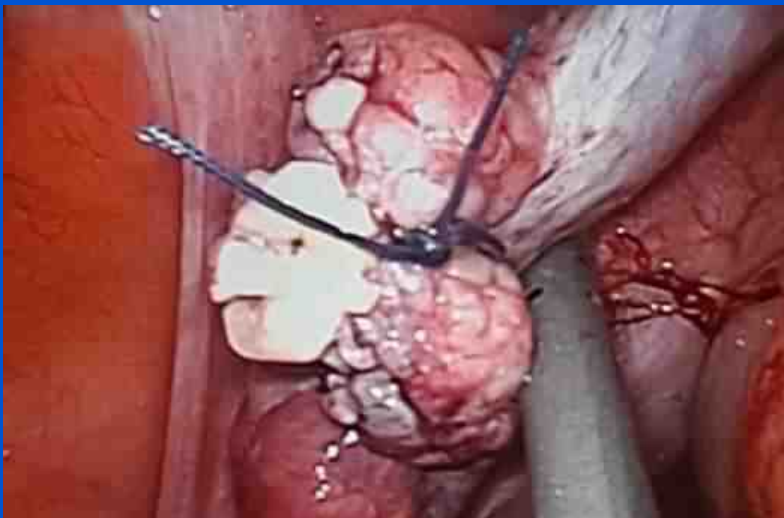
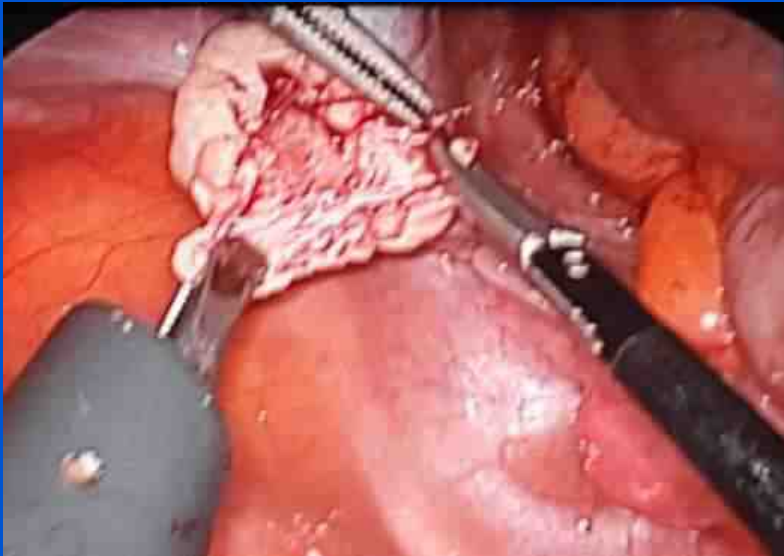




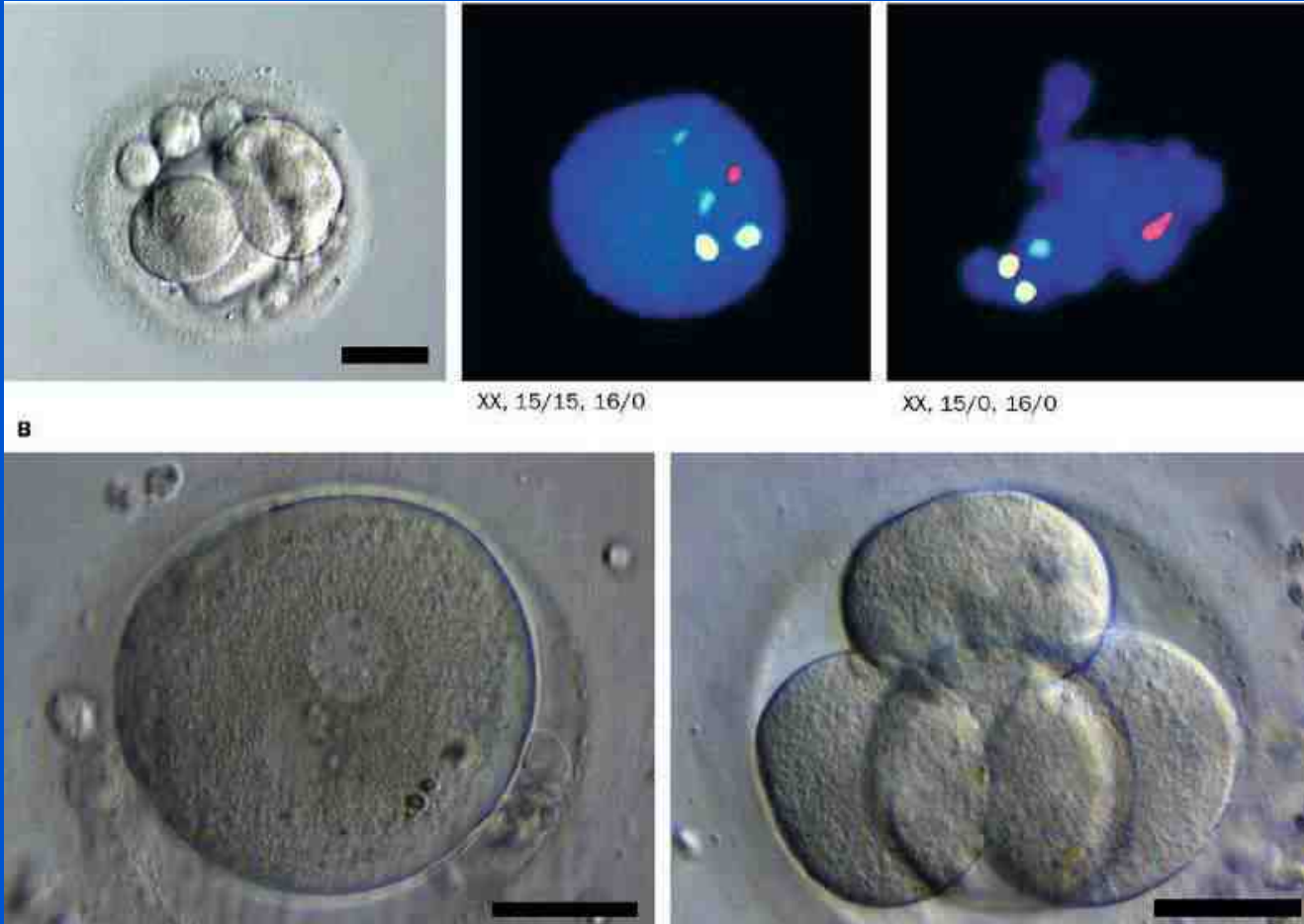
Meme Kanseri – Overyan Transplantasyon



Meme Kanseri – Overyan Transplantasyon



Transplantasyon Sonrası ART Heterotopik Alan



M1 \Rightarrow IVM/MII \Rightarrow ICSI, 4-hücreli embriyo

Oktay, Lancet, 2004

First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy

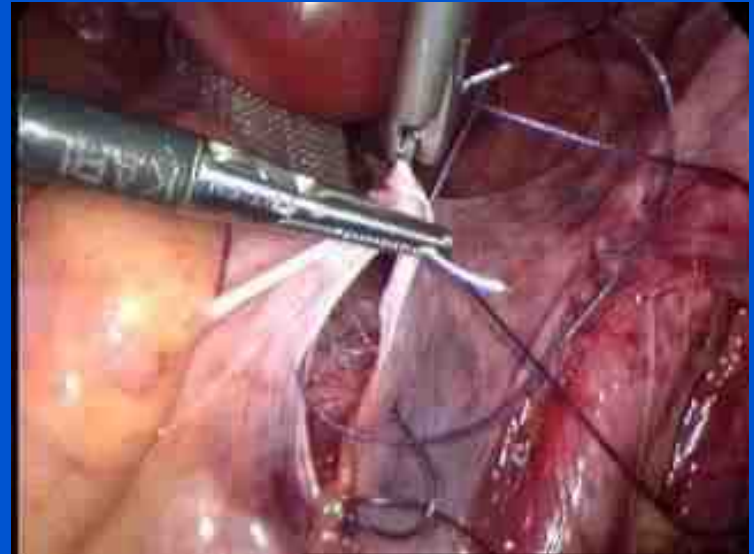
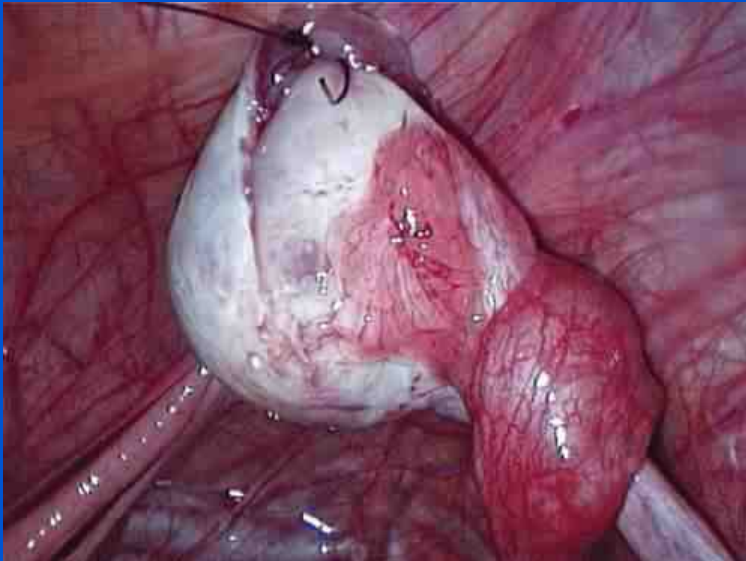
C.J. Stern^{1,*}, D. Gook¹, L.G. Hale¹, F. Agresta¹, J. Oldham², G. Rozen³, and T. Jobling⁴

¹Reproductive Services, Melbourne IVF and Royal Women's Hospital, Parkville, VIC, Australia ²Women's Ultrasound East Melbourne, East Melbourne, VIC, Australia ³Reproductive Services, Royal Womens Hospital, Parkville, VIC, Australia ⁴Gynaecological Oncology, Monash Health, Moorabbin, VIC, Australia

- 21 yaşında granuloza hücreli tümör
- Bilateral ooforektomi
- Transplantasyon 7 yıl sonra
- ART ile gebelik

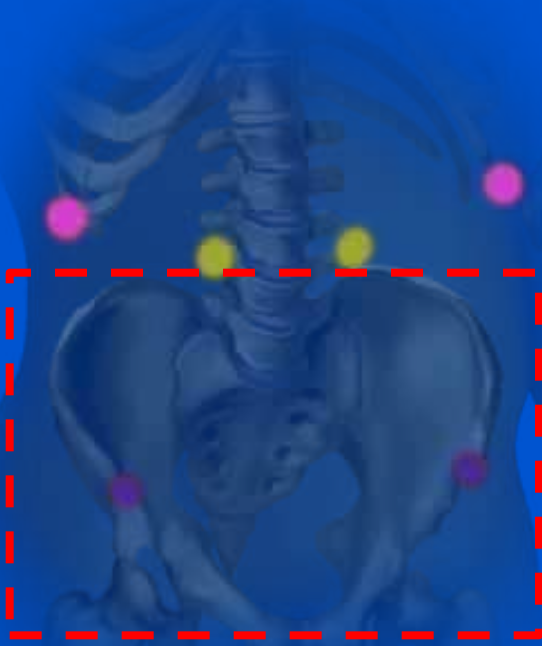
Overyan Transpozisyon

- Pelvik radyoterapi alan hastalar (8-20 Gy cut-off)
- Lateral overyan transpozisyon
- Medial overyan transpozisyon (uterus arkası)

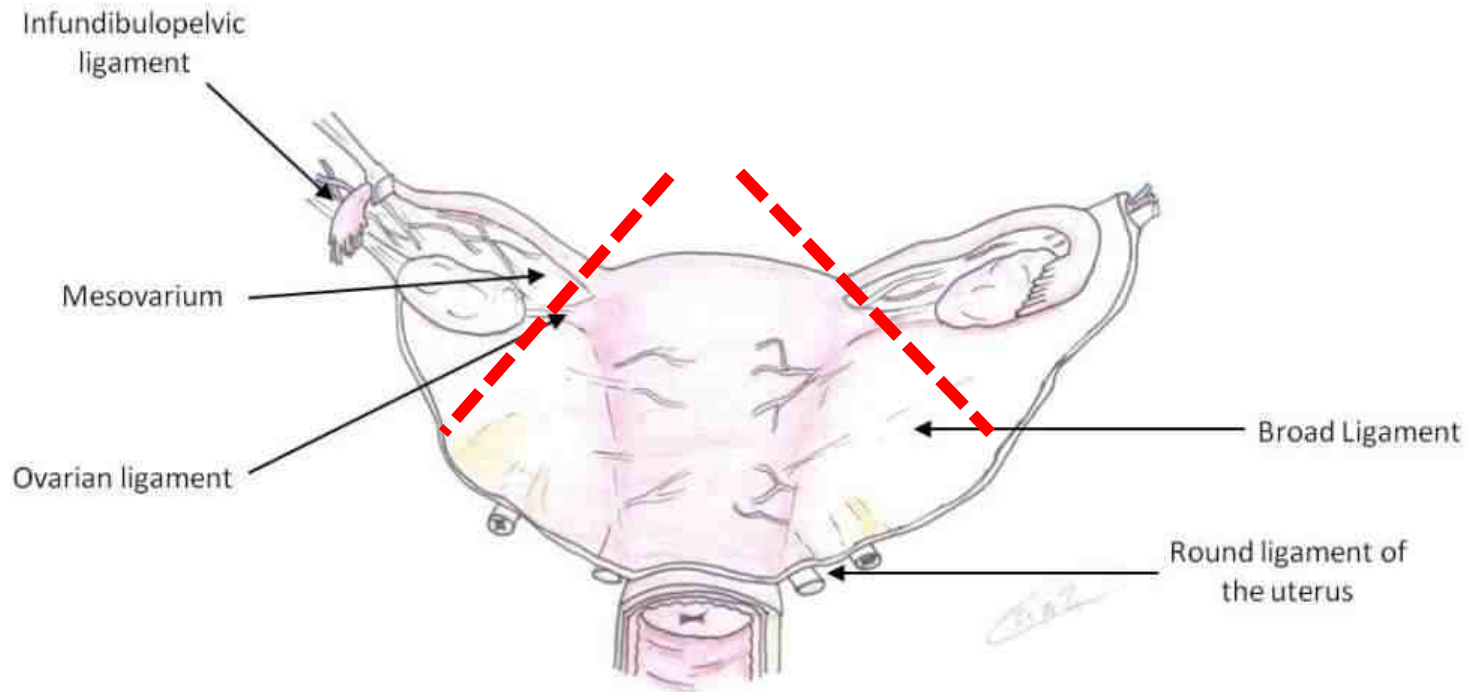


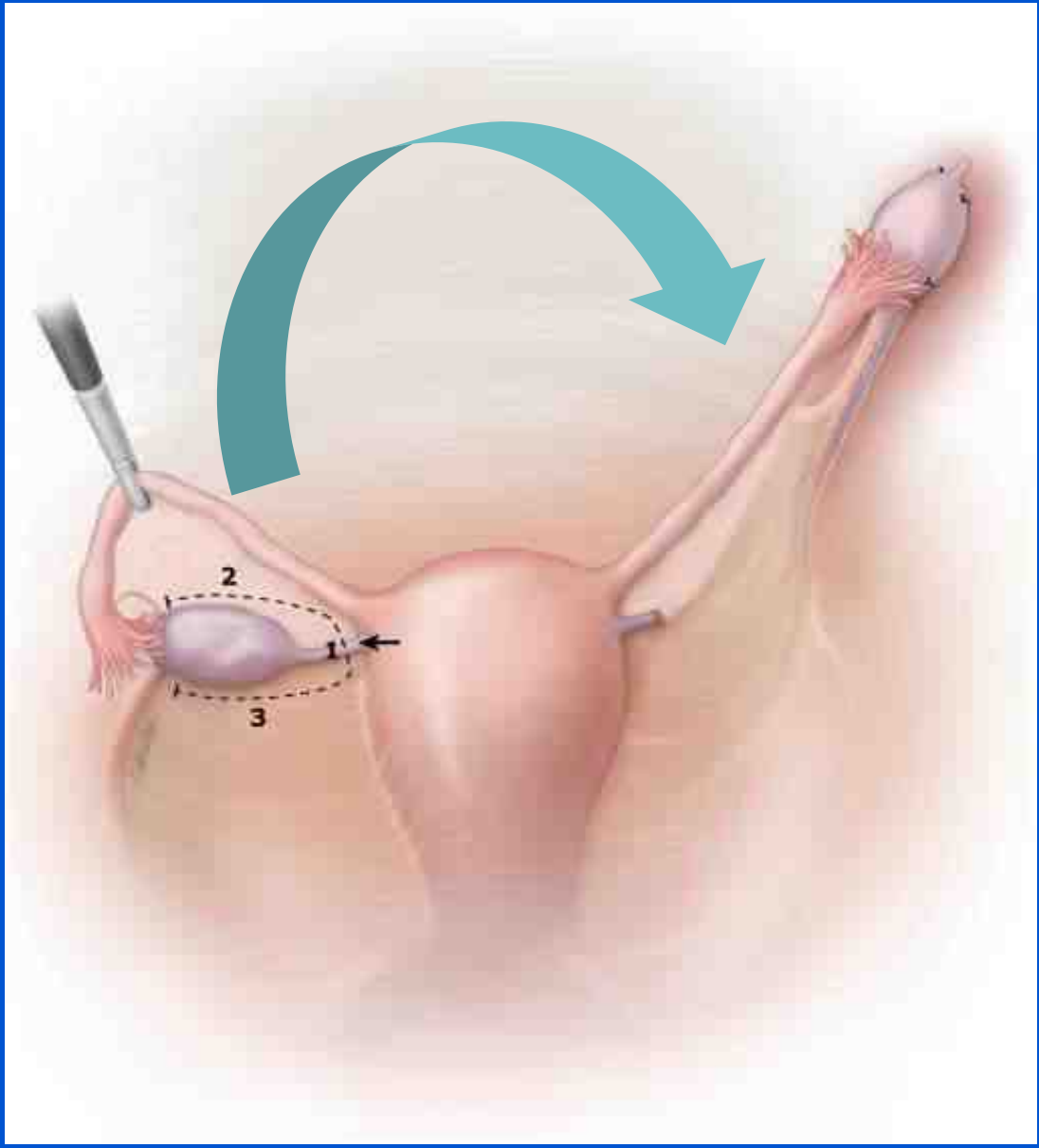
Overyan Transpozisyon Alanları

- Parakolik bölge
- Ön psoas kası
- Alt parakolik bölge
- Uterus arkası

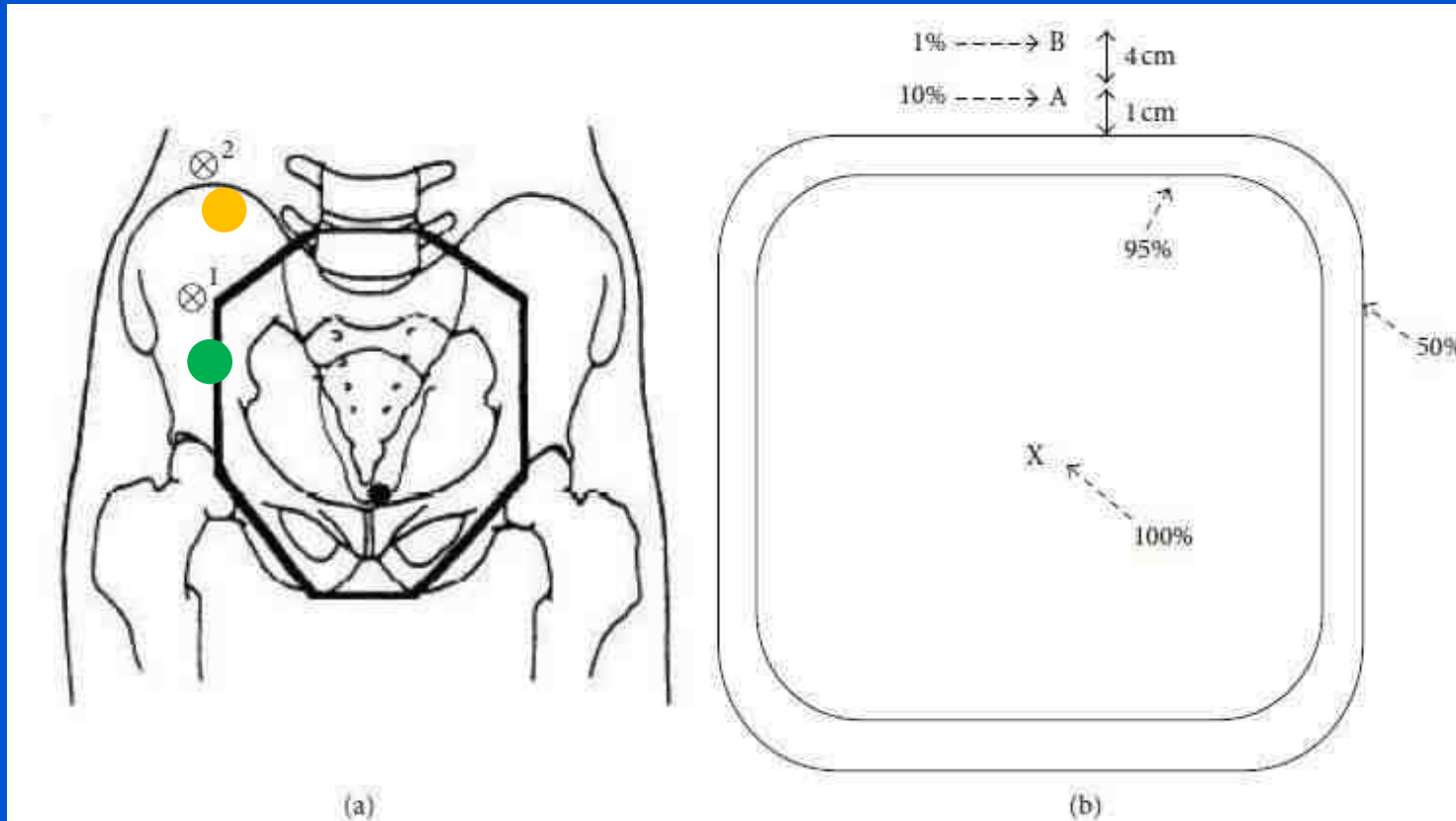


Overyan Kan Akımı



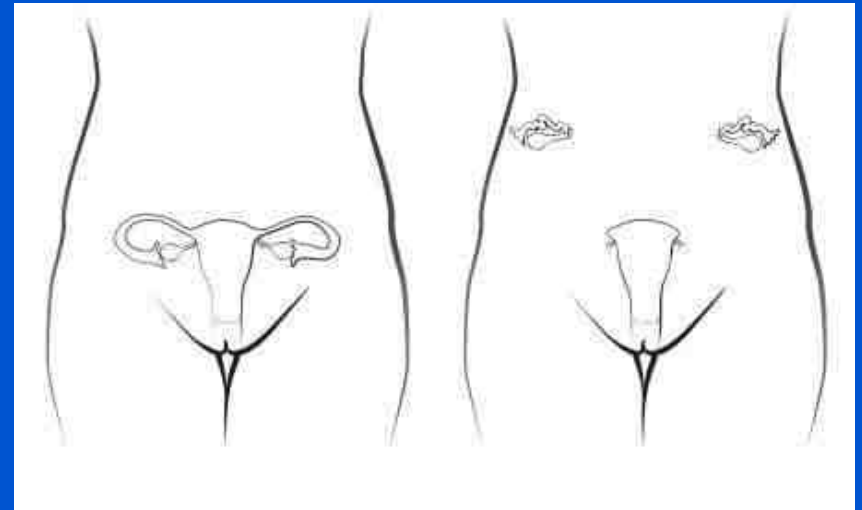
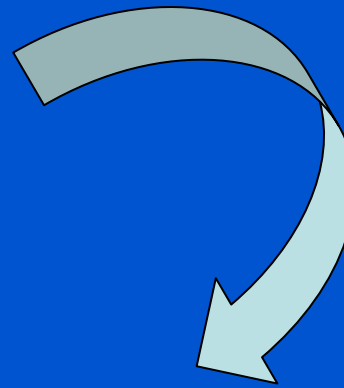
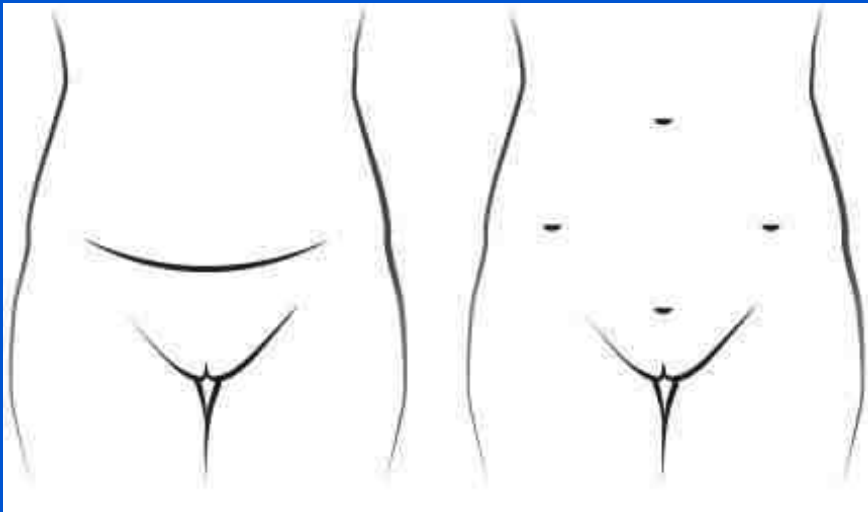


Lateral Ovaryan Transpozisyon



Merkezden 10 cm \rightarrow %10 RT doz

Lateral Ovaryan Transpozisyon



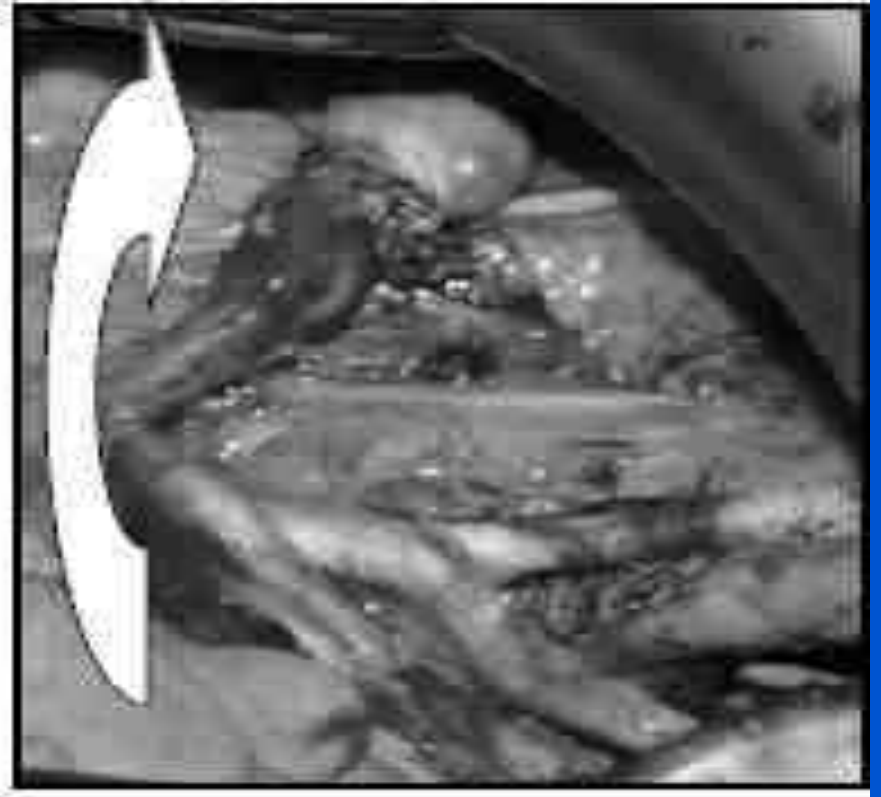
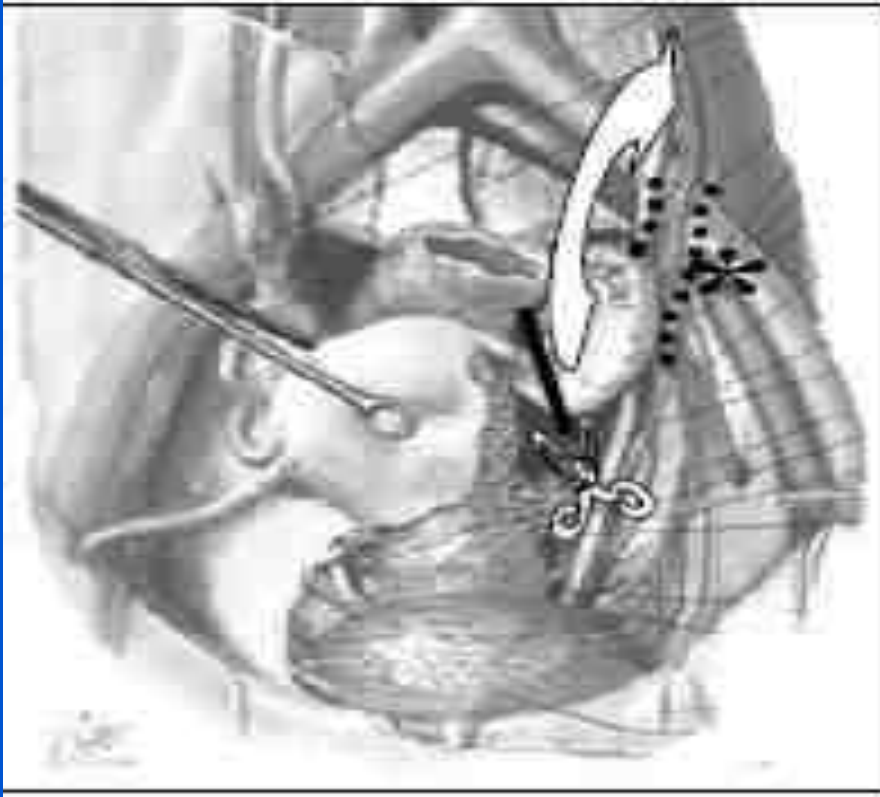
Overyan Transpozisyon – İşlem

- Umbilikus trokarının yerleştirilmesi
 - Üst RT sınırının 2-3 cm üzeri
 - Genellikle umbilikusun 2-3 cm üzeri
- İkincil trokarlar aynı düzeyde, ya da hafif aşağıda yerleştirilir
- Abdominal kavite dikkatlice incelenir
- Üreter çizgileri gözlenmeli
- Oosit /ovarian doku kriyo işlemleri değerlendirilmeli

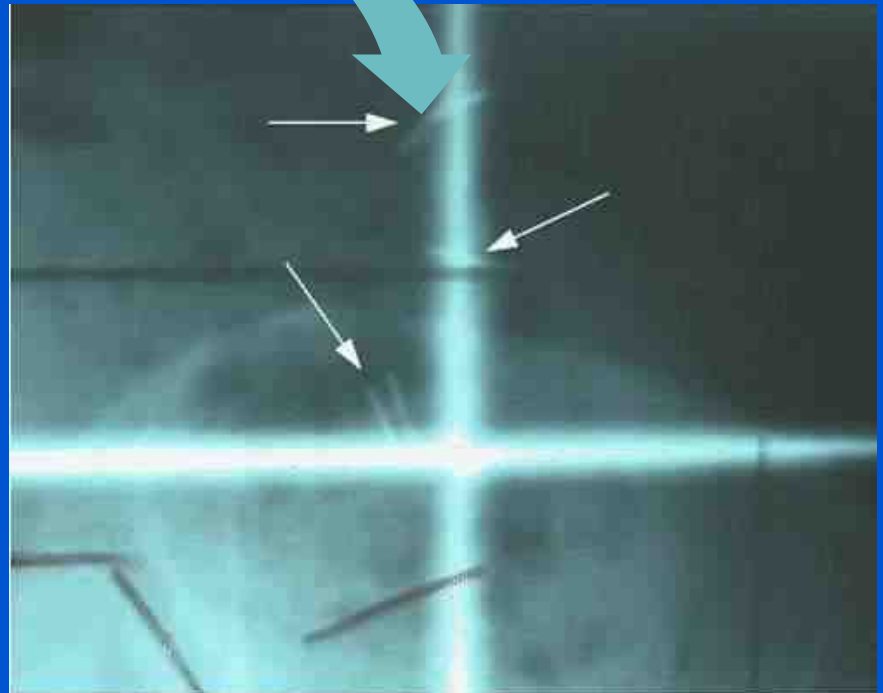
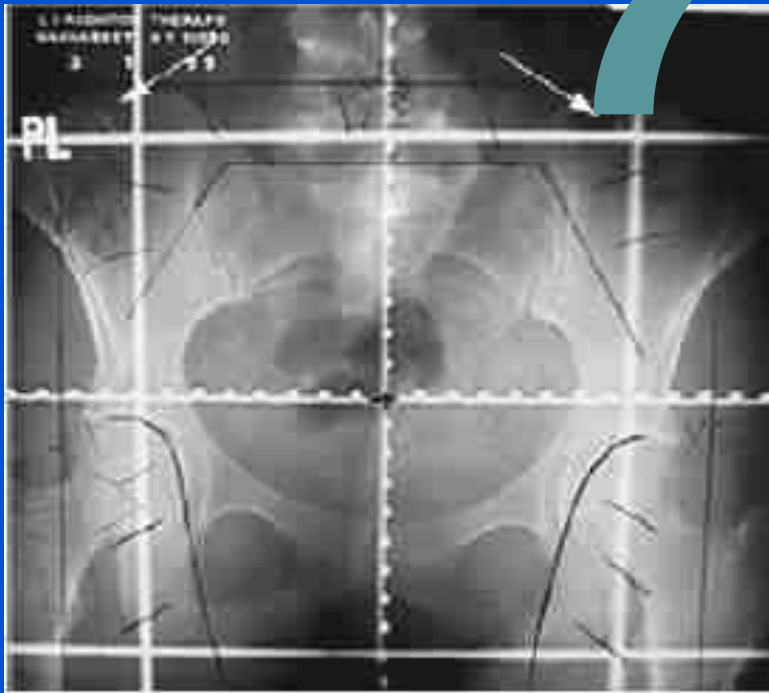
Overyan Transpozisyon – İşlem

- Utero overyan ligamentler ayrılarak mesoovaryum serbesleştirilmeli
- Anterior süperior iliak çizgiye kadar periton serbestleştirilmeli
- Absorbe olmayan sütürler ile overler kanlanma bozulmadan lateral peritoneal duvara – parakolik alana suture edilmeli
- Broad ligament alanında boşluk kapatılmalı
- Over bölgesi hemoklip ile belirlenmeli

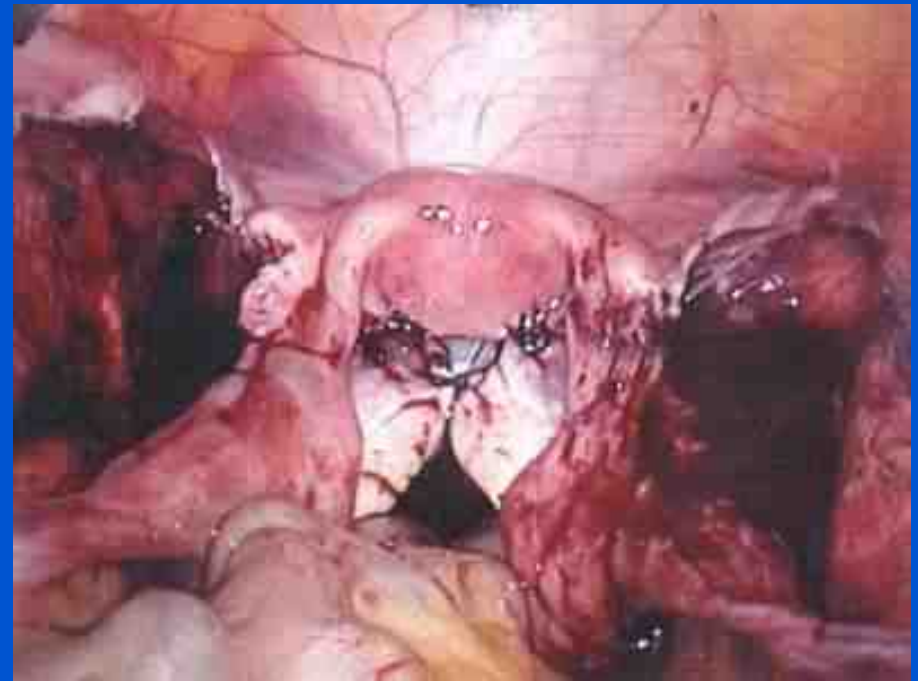
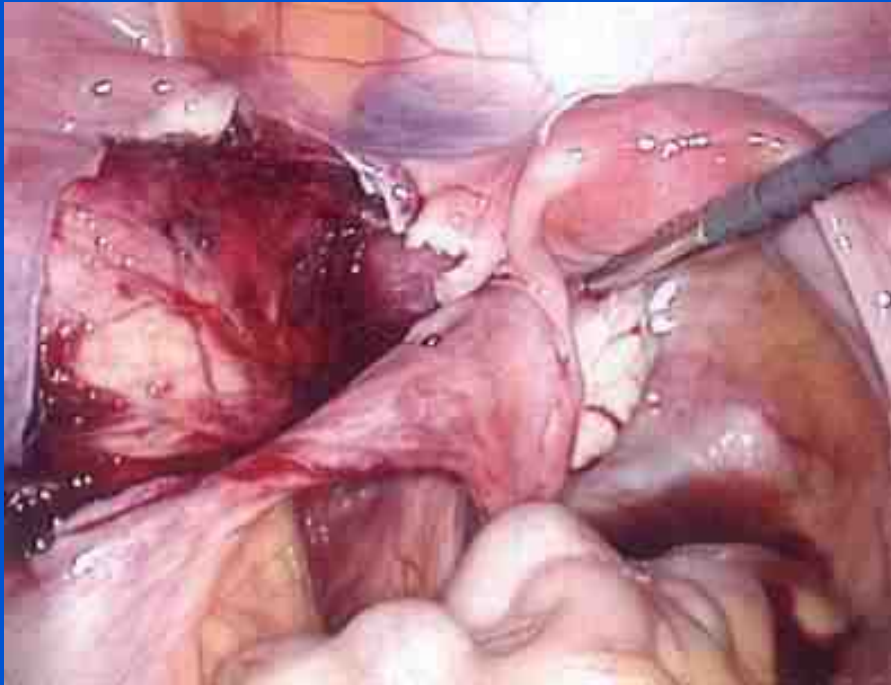
Lateral Ovaryan Transpozisyon



Lateral Ovary Transposition



Medial Ovaryan Transpozisyon



Overyan transpozisyon

Saçılan radyasyon

- Brakiterapi - 4500 cGy
- Saçılan radyasyon 175 cGy (40-370cGy)
- İyatrojenik POF →%10 (takip 2 yıl)
- 40 yaşın altında POF yok

Medial vs Lateral Ovaryan Transpozisyon

Lateral OT		Medial OT	
Menstruasyon	Amenore	Menstruasyon	Amenore
57 (%86)	9 (%14)	11 (%50)	11 (%50)

Overyan transpozisyon

Kemoterapi etkisi

Overyan fonksiyon	Kemoterapi	
	0-2 siklus	>2 siklus
Var	5	0
Yok	1	4

Kemo: MOPP, ABVD, MOPP/ABV

S Stan Williams, Ramey D. Littell, Nancy P. Mendenhall CANCER, 1999

Overyan transpozisyon

Komplikasyonlar

- Vasküler hasar– kan damarlarının torsiyonu
- Kronik over ağrısı
- Ovaryan kist
- Pelvik bölgeye overlerin geri dönüşü
- Başarı %16-90

SONUÇ

- Overyan kriyo ve transplantasyon henüz standart bir teknik değildir
- Overyan kriyo, KOH-oosit ya da embriyo kriyoprezvasyon ile birlikte yapılabilir
- Laparoskopik overyan transpozisyon pelvik RT alan hastalarda başarılı bir şekilde uygulanabilir

Pregnancy following transplantation

- ART in 12 patients \Rightarrow 65 oocytes in 72 cycles
- Pregnancy/cycle \Rightarrow 6.9% (5/72)
- Live birth/cycle \Rightarrow 2.8% (2/72)
- Post-transplant ovarian function 9 months- 7 years
- AMH<1ng/ml (spontaneous pregnancy in patients)