

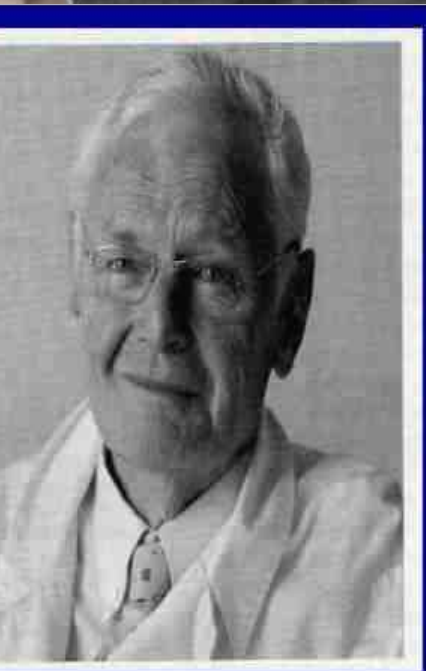
Fertility Preservation in Female Cancer Patients



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Oncofertility for gynecologic and non-gynecologic cancers: Fertility sparing in young women of reproductive age

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Contents

Main Goal of Cancer Therapy

- **High Cure (PFS, OAS)**
- **Low morbidity**
- **Quality of life**
 - Cosmetic appearance**
 - Sexual life**
 - Mood**
 - Fertility preservation**

Main Requirement of Fertility Preservation



Preserving of the uterus
Preserving at least one ovary
If indicated freezing
oocyte,embryo or ovarian tissue

All Therapeutic Modalities in Cancer Treatment

are associated with infertility

- Radiation**
- Radical surgery**
- Chemotherapy...**

Objectives of Fertility Preservation Approach

- **Similar oncologic outcomes to standard therapy**
- **Favorable obstetric outcome**
- **Low morbidity and cost**

Benefits >>>>> Risks

- | | |
|---|--|
| <ul style="list-style-type: none">• Preservation of fertility• Maintenance of endocrine function | <ul style="list-style-type: none">• Increase in probability of recurrence and death• Additional surgery |
|---|--|

Available Fertility Preservation Strategies

Cryopreservation

- Sperm
- Oocyte (Slow vs. Vitrification)
- Embryo (Slow vs. Vitrification)
- Ovarian Tissue Preservation
- Primordial Follicle *in vitro* maturation

Medical

- GnRH agonist

Surgical

- Less Radical (Organ sparing surgery)
- Ovarian Transposition (GYN ca, colorectal Ca, spinal ca...)
- Transplantation of Cryopreserved ovary (ortho & heterotopic transplantation)
- Uterus Transplantation
- Uterus&ovarian transplantation(exper)

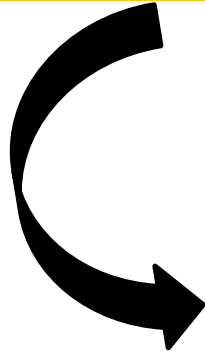
Candidate Selection is Important

- **Age <35-40 ? Yrs**
- **Overall health status**
- **Origin of tumor, Stage, Grade**
- **Chance of 5 years OAS**
- **Therapy related premature ovarian insufficiency
(Cryopreservation)**
- **Informed consent from patient, parents, partner
(USO- high dose Gn- secondary POI)**
- **Previous infertility problems**
- **Close follow up**

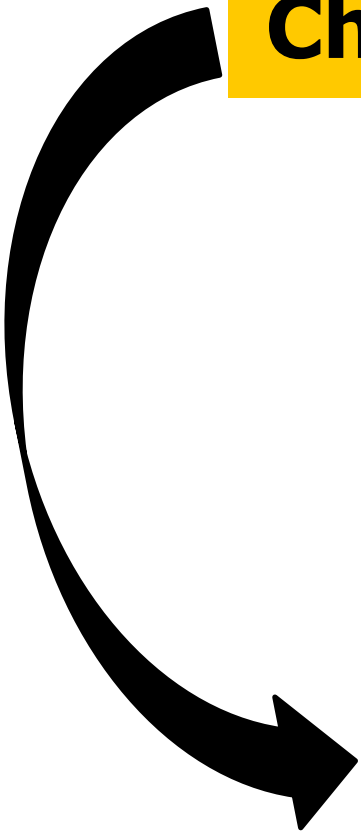
Hematologic Malignancies



Chemotherapy ± Radiotherapy

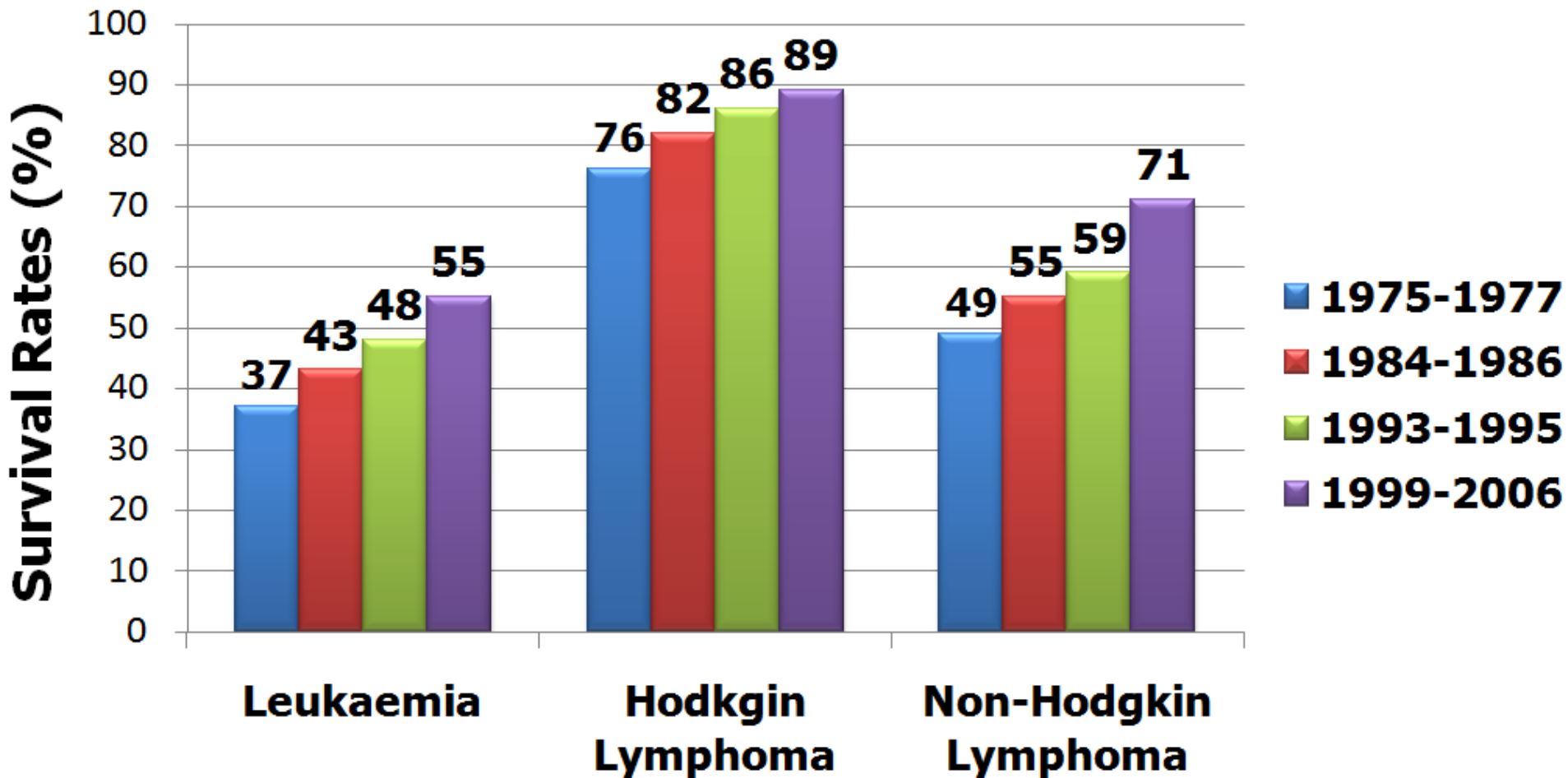


GonadoToxicity



**Impaired Reproductive
Function**

Improved 5 yrs OAS For Hematologic Malignancies



Fertility Preservation in Hematologic Malignancies

- Time vs. Disease Burden
- Ovarian Tissue Preservation
- Oocyte CryoPreservation
(Needs Ovarian stimulation)
- Primordial Follicle + IVM

-

A black horizontal oval containing the text "IVF" in bold yellow capital letters.

IVF

Gynecological Cancer rates <40y

CANCERS

%

Breast Ca

7

Cervical Ca

43*

EOC

3-17

Endometrial Ca

2-14

BOT

30

* In developed countries

Breast Cancer

- **25% prior to menopause**
- **7% under age 40**
- **60% are hormone sensitive**
- **5 yrs OAS rates**

Local disease 98%

Regional disease 84%

Breast Cancer

- **E2 & it's metabolites ↑ disease progression**
- **Animal study Estrogen rec neg - tm progression**
- **Conventional stimulation --XX**
- **Aromatase inh-Letrozole (oktay 2006)**
- **SERM – Tamoxifen (oktay 2003)**
- **Letrozole + GnRH**

Breast Cancer

- **Stimulation & oocyte harvest**
Do not delay treatment (Baynosa 2009, Madrigano 2007)
 - **Treatment modification**
 - **Short-term modified protocols (10 days delay)**
(GnRH agonist rather than hCG)
- E ↑↑↑ in ovulation induction only 10 days & low E2 levels**
- No effect on OAS , DFS** (Azim et al., 2008)

FSS in Ovarian Malignancies (EOC, BOT,MOGCT, Sex Cord Stromal)

- **Adequate surgical staging**
- **Removal of affected ovary and tube**
- **Preservation of the uterus and ovarian tissues in one or both ovaries**
- **Finally evaluation of normal appearing contralateral ovary* and endometrium (D&C)****

* Synchronised tumor and occult metastases (about%2.5-3)

* Endometrioid type of epithelial tumors

Indication for FSS in EOC

- 1. **Stage Ia Grade 1**
Stage Ia Grade 2 (limited)

- 2. **Stage Ic, Grade 3, Clear cell**
**+
Chemotherapy**

Main Problems in FSS in EOC

- A) In preserved ovary**
 - Occult metastasis**
 - Relapse in preserved ovary**

- B) Relapse related death due to the preservation of ovary, uterus**

- C) Is there a place of complementary surgery after childbearing**

FSS Does Not Affect Survival in Early Stage EOC

- **Survival after FSS in patients
with early ovarian cancer**



- **Without chemo is about 94%**

Oncologic & Obstetric Outcome – Inv.EOC

	Patients	Pregnancies	Birth	Recurrence	Death
Colombo et al	56	25	16	3	2
Zanetta et al	84	33	22	5	3
Duska et al	6	2	2	1	1
Morice et al	34	10	7	10	4
Schilder et al	52	17	26	5	2
Park et al	62	22	22	11	6
Raspagliesi et al	10	3	3	0	0
Colombo et al	24	7	6	7	2
Total	328	119(%36)	104(%87)	42(%13)	20(%6)

FSS in Borderline Tumors of the Ovary

- **15% of all EOC** (Park et al., 2009)
- **Young age**
- **Early stage**
- **95% serous – mucinous**
- **Do not require add. CT**
- **Overall survival 95 %**

Ovarian procedures in BOT

- BSO (very rare)
- USO
- Cystectomy (?)
- Partial excision*

*at least 5mm TF border

Effect of surgical staging on 539 patients with borderline ovarian tumors: A Turkish Gynecologic Oncology Group study

Abstract

Send to:

Gynecol Oncol. 2013 Dec;131(3):546-50. doi: 10.1016/j.ygyno.2013.08.038. Epub 2013 Sep 7.

Effect of surgical staging on 539 patients with borderline ovarian tumors: a Turkish Gynecologic Oncology Group study.

Guvenal T¹, Dursun F, Hasdemir PS, Hanhan M, Guven S, Yetimalar H, Goksedef BF, Sakarya DK, Doruk A, Terek MC, Saatli B, Guzin K, Corakci A, Deger E, Celik H, Cetin A, Ozsaran A, Ozbakkaloglu A, Kolusari A, Celik C, Keles R, Sagir FG, Dilek S, Uslu T, Dikmen Y, Altundag O, Ayhan A.

Author information

Abstract

OBJECTIVE: The objectives of this study were to examine demographic and clinicopathologic characteristics and to determine the effects of primary surgery, surgical staging and the extensiveness of staging.

METHODS: In a retrospective Turkish multicenter study, 539 patients, from 14 institutions, with borderline ovarian tumors were investigated. Some of the demographic, clinical and surgical characteristics of the cases were evaluated. The effects of type of surgery, surgical staging, complete or incomplete staging on survival rates were calculated by using Kaplan-Meier method.

RESULTS: The median age at diagnosis was 40 years (range 15-84) and 71.1% of patients were premenopausal. The most common histologic types were serous and mucinous. Majority of the staged cases were in Stage IA (73.5%). 242 patients underwent conservative surgery. Recurrence rates were significantly higher in conservative surgery group (8.3% vs. 3%). Of all patients in this study, 294 (54.5%) have undergone surgical staging procedures. Of the patients who underwent surgical staging, 228 (77.6%) had comprehensive staging including lymphadenectomy. Appendectomy was performed on 204 (37.8%) of the patients. The median follow-up time was 36 months (range 1-120 months). Five-year survival rate was 100% and median survival time was 120 months. Surgical staging, lymph node sampling or dissection and appendectomy didn't cause any difference on survival.

CONCLUSION: Comprehensive surgical staging, lymph node sampling or dissection and appendectomy are not beneficial in borderline ovarian tumors surgical management.

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KEYWORDS: Appendectomy; Borderline; Lymphadenectomy; Ovarian tumor; Surgical staging

Obstetric & Oncologic Outcome - BOT

	Patients	Pregnancies	Live Births	Recurrence	Death
Zanetta et al	189	44	N/A	35	0
Lim-Tan et al	35	8	6	6	0
Morice et al	44	17	10	9	0
Boran et al	62	13	10	4	0
Fauvet et al	162	30	18	27	0
Donnez et al	16	12	12	3	0
Seracchiolo et al	19	6	6	1	0
Carnatte et al	17	8	8	9	0
Morris et al	43	25	16	14	1
Gotlieb al	39	22	21	3	0
TOTAL	626	185(%30)	107(%58)	111(%18)	1(%0.2)

Germ Cell Ovarian Tumors

- **Young women & Adolescent girls.**
- **Unilateral often**
- **All need adjuvant chemotherapy , except stage-I, low grade immature teratomas and stage-IA dysgerminomas**
- **Chemo(platin based) is marked gonadotoxic, fertility preservation should be considered(Oocyte, embryo) accordingly.**
- **High Dose Gonadotrophin induction is needed.**


Obstetric & Oncologic Outcome - GCT

	Patients	Pregnancies	Live Births	Recurrence	Death
Gershenson et al	40	22	22	3	2
Kanazawa et al	21	11	9	1	1
Low et al	74	19	14	7	2
Gershenson et al	71	37	30	10	4
Zanetta et al	138	41	28	16	3
Perrin et al	45	8	7	4	2
Tangir et al	64	47	38	5	3
TOTAL	453	185(%41)	148(%80)	46(%10)	17(%3.8)

Endometrial Cancer and EIN/AEH

- **Most frequent Gyn.Ca**
- **25% premenopausal**
- **5% under 40 age**
- **Type I good prognosis (PCOS)**
- **Grade I, EPR +**
- **Cure rate %95**

Fertility Sparing Treatment in Endometrial Cancer

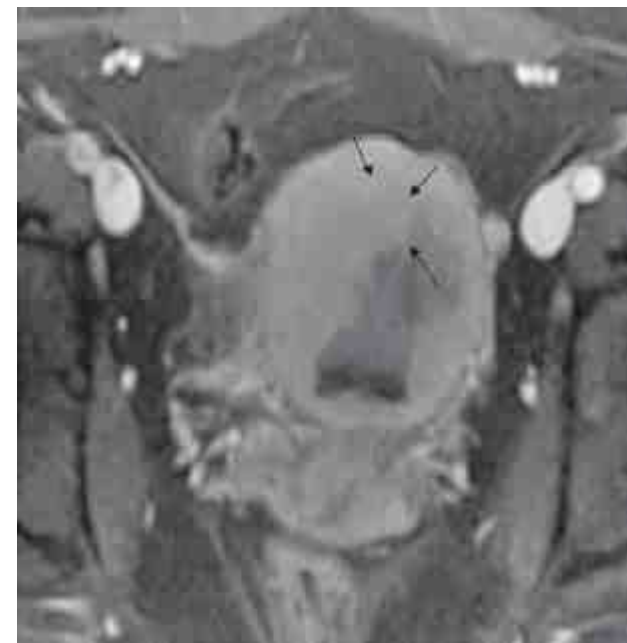
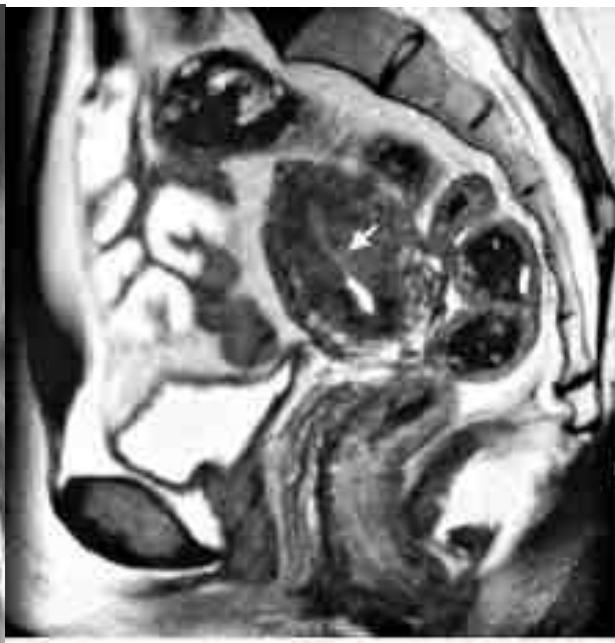
- **At young age**
 - **Well differentiated End. Ca**
 - **Stage IA, Grade I-II**
 - **Progesterone therapy**
 - **Evaluation of end. with 3-6 mts interval**
 - **Fertility desire**
- 

Pretreatment Evaluation

- **History (infertility, HNPPCC, sync tm...)**
- **Physical Examination**
- **TVUSG**
- **D&C**
- **MRI enhanced**
 - **abdominopelvic**
 - **endovaginal coil**
- **Ca-125**

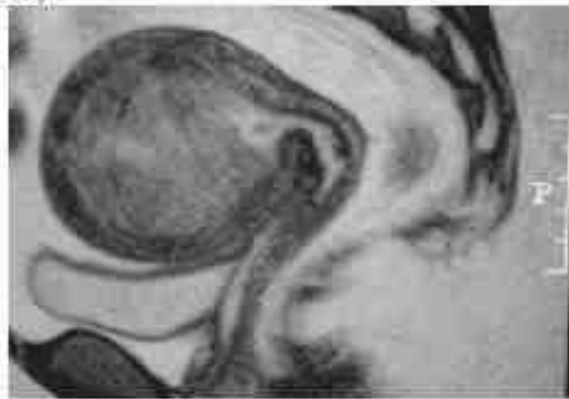
Staging (Laparoscopy or Laparotomy)

Controversial??



MRI Sensitivity %80 Specificity %100

A)



B)



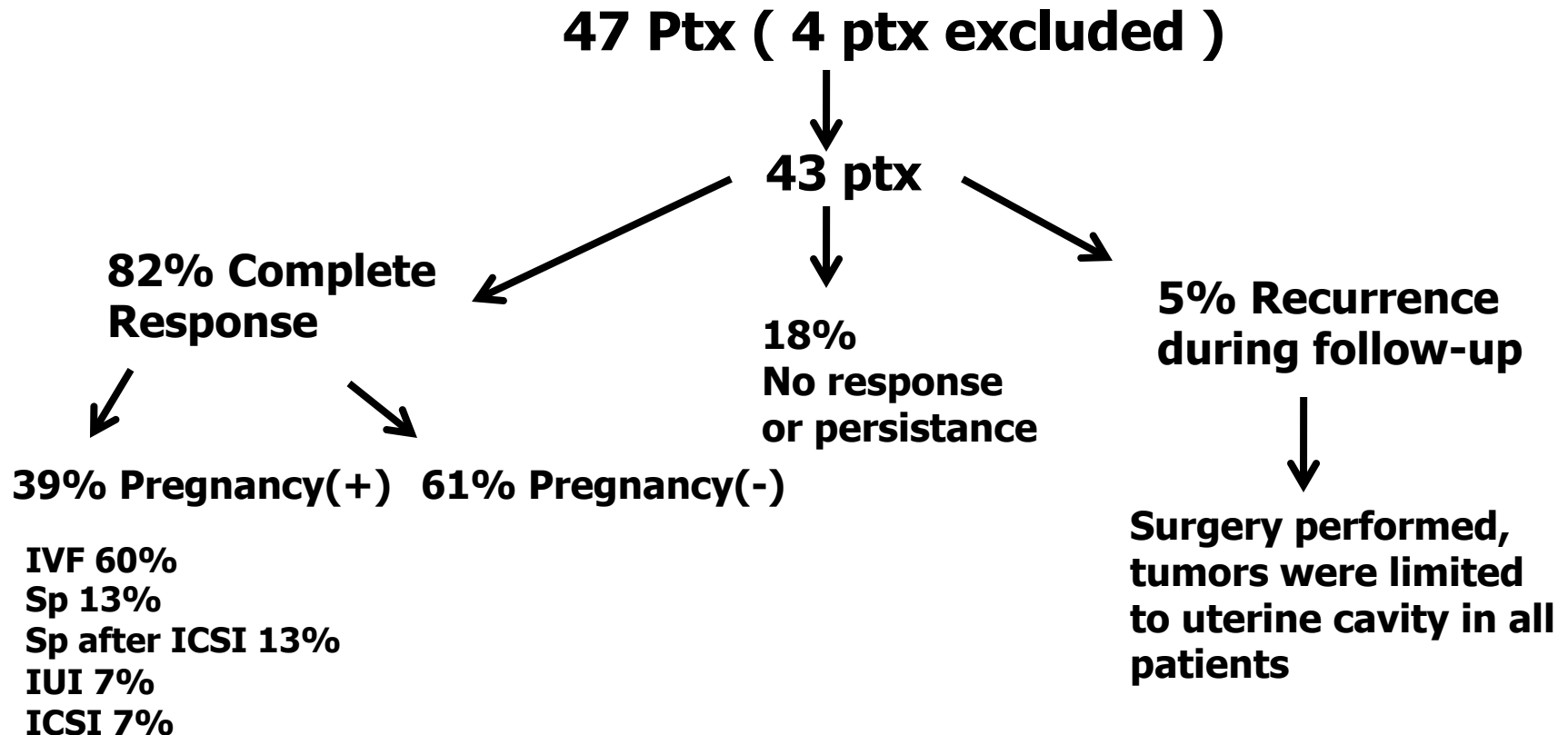
Before and After Treatment

Progesteron Therapy

- **MPA 200-600 /mg/ day**
- **Megestrol Acetate 40-160 /mg/day**
- **Levonorgestrel IUD / Prog**
- **Response Rate** **%**
 - A. Hyperplasia/EIN** **83 – 94**
 - End. Ca** **57 - 75.6**
- **Duration of Treatment** **mts**
 - Range** **3-6**
 - Median** **9**
- **Recurrens rate** **%**
 - A.Hyperplasia** **13**
 - End. Ca** **11-50**

A Turkish Gynecologic Oncology Group study of fertility-sparing treatment for early-stage endometrial cancer [☆] *International Journal of Gynecology and Obstetrics* 119 (2012) 270–273

Polat Dursun ^{a,*}, Serkan Erkanli ^a, Ahmet Barış Güzel ^b, Murat Gultekin ^a, Nefise Cagla Tarhan ^a, Ozden Altundag ^a, Fuat Demirkiran ^c, Tugan Beşe ^c, Yusuf Yildirim ^d, Gurkan Bozdag ^e, Hakan Yarali ^e, Tayyup Simsek ^f, Bulent Ozcelik ^g, Firat Ortaç ^h, Salih Taskin ^h, Tevfik Guvenal ⁱ, Nejat Ozgul ^j, Ali Haberal ^a, M. Ali Vardar ^b, Murat Dede ^{j,k}, Mufit Yenen ^{j,k}, Aytakin Altintas ^b, Macit Arvas ^c, Ali Ayhan ^a



OUTCOMES - PROGESTERON THERAPY in ENDOMETRIUM CANCER

	Patients	Regression	Relapse	Live Births	Progesterone
Randal and Kurman	12	9	1	6	Megestrol or MPA
Duska et al	12	10	1	5	MPA
Imai et al	14	8	3	3	MPA
Kaku et al	12	9	2	1	MPA
Wang et al	9	8	4	3	Megestrol
Niwa et al	12	12	8	5	MPA
Lowe et al	2	2	0	8	Megestrol
Sardi et al	4	3	0	3	MPA
Yang et al	6	4	2	2	Megestrol
Farhi et al	4	3	1	2	Progestin
Gotlieb et al	13	13	6	9	Megestrol
TOTAL	100	81(%81)	28(%28)	47(%47)	

Cervical Carcinoma

**10%-15% of diagnosed
during the childbearing
years**

**43% of all cases younger
than 45 years of age**

Selection Criteria-1

Fertility desire;

Age < 40 years;

No evidence of local/distant metastasis;

Sq/Adeno (except neuroendocrin type)

Experienced team

Selection Criteria-2

**Stage Ia1 +/- LVSI, Ia2,
Ib1;**

Tumor size < 2 cm;

Invasion less than 1 cm

**Disease located primarily
on the ectocervix**

Authors		n	Parametrial inv. (%)
Kinney	1995	83	0.0
Covens	2002	536	0.6
Stegeman	2007	103	0.0
Wright	2008	270	0.4
Frumovitz	2009	125	0.0
Total		1117	0.3

Conservative management of early stage cervical cancer: is there a role for less radical surgery? [Schmeler KM](#), [Frumovitz M](#), [Ramirez PT](#). *Gynecol Oncol*. 2011 Mar;120(3):321-5.

Type of Intervention

- **Conisation/LEEP**
- **Trachelectomy***
- **Trachelectomy following neoadjuvant chemotherapy**
- **Ovarian Transposition**
- **Lymphadenectomy**

*vaginal/abdominal/endoscopic



IA1 LVSI (-) CONE

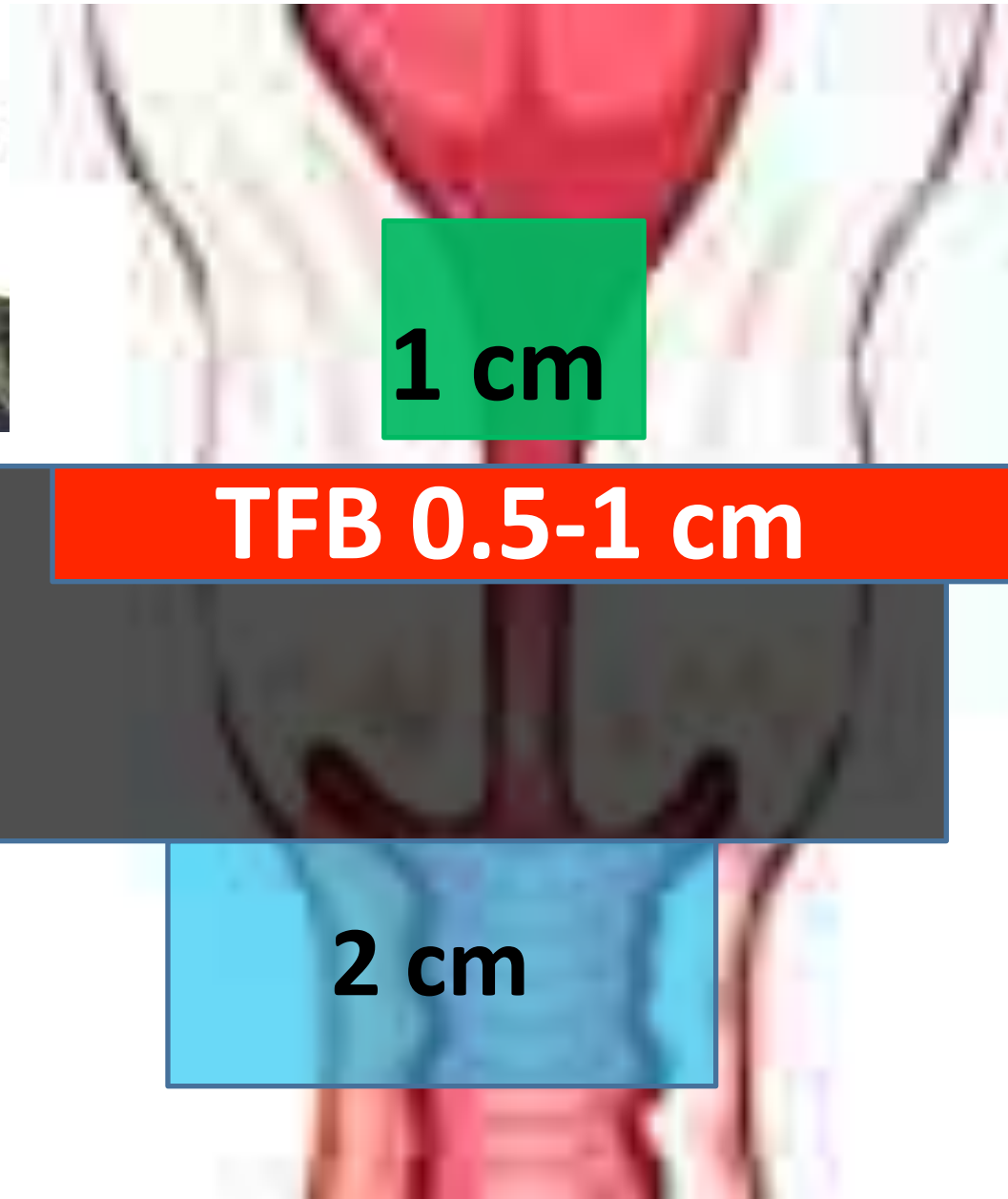


- **Tumor free margin and post-cone negative ECC**
- **Positive margin or positive ECC**



RE-CONE





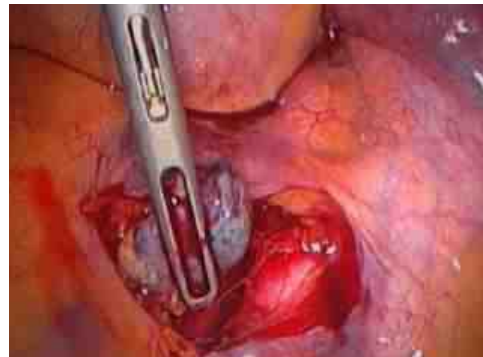
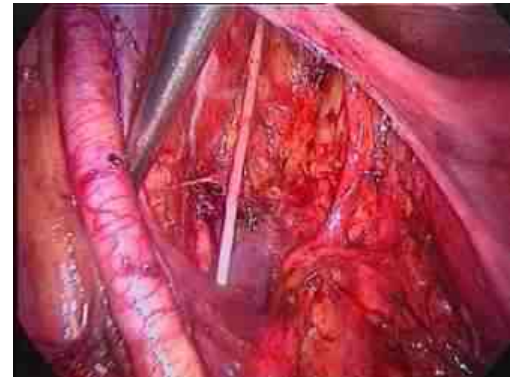
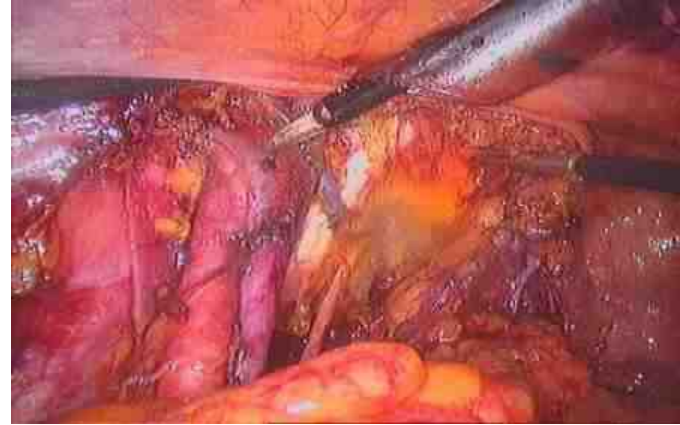
1 cm

TFB 0.5-1 cm

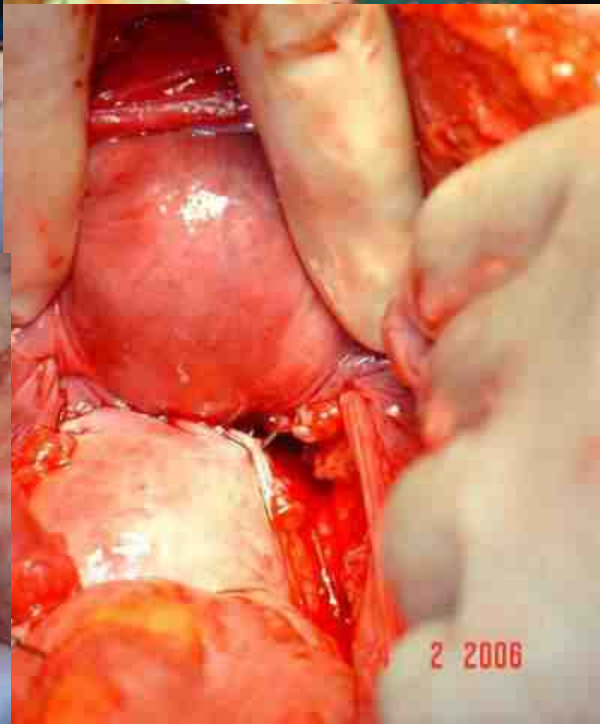
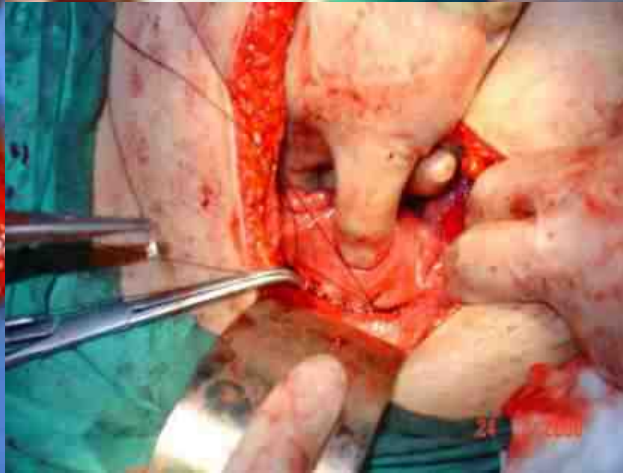
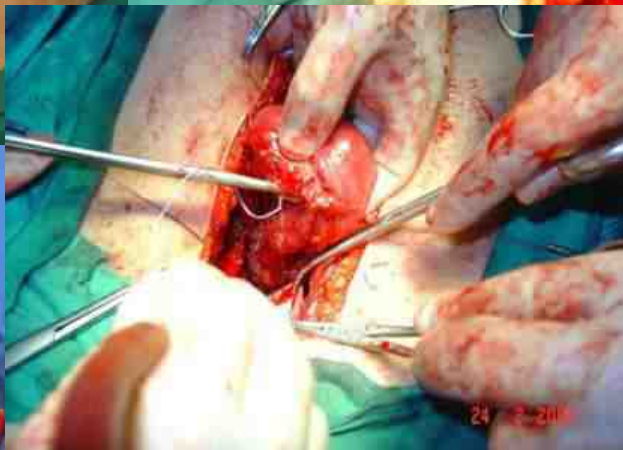
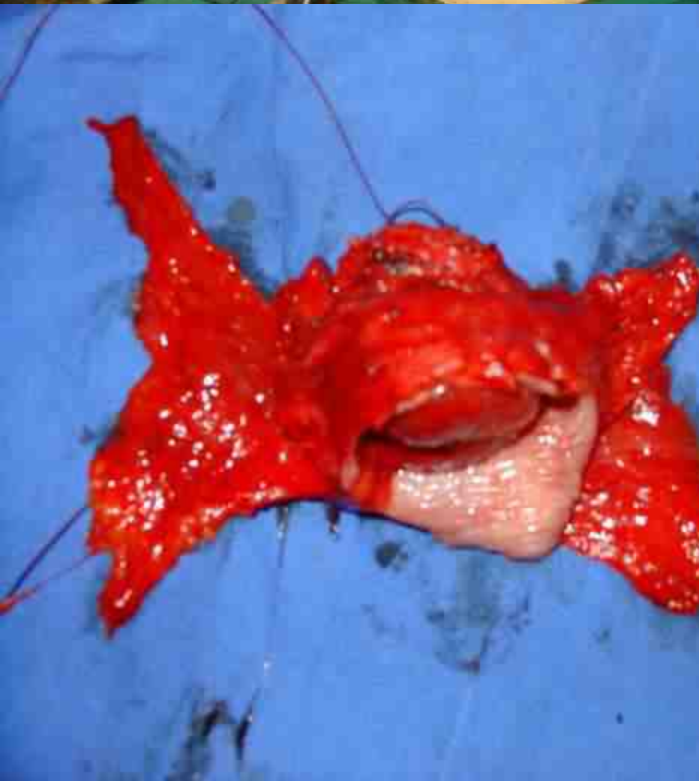
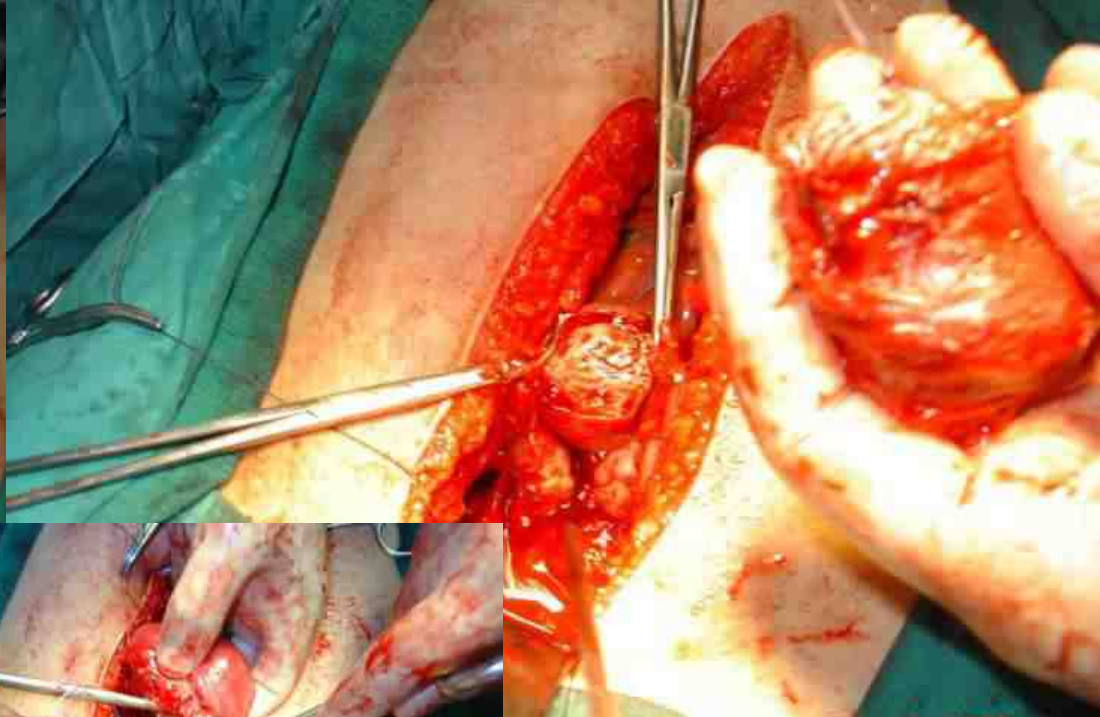
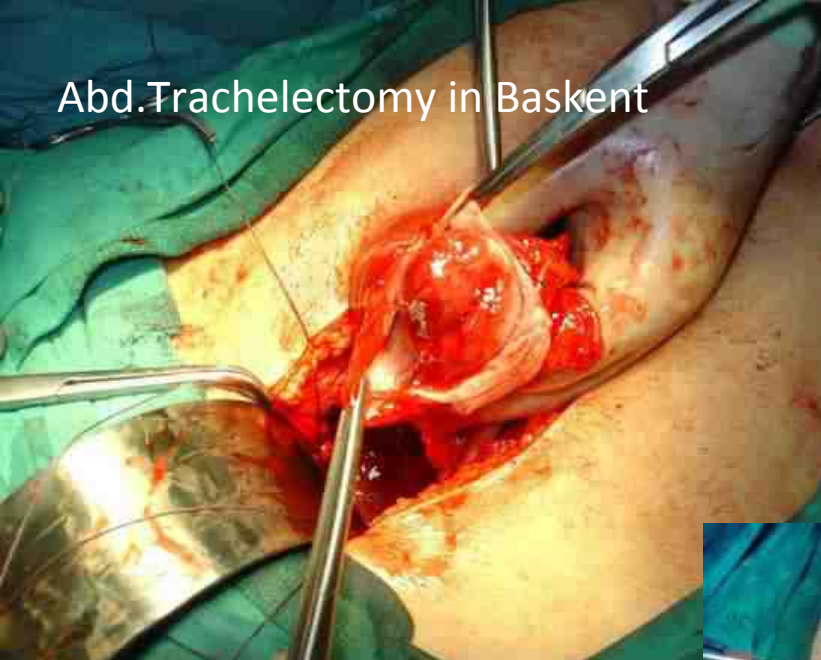
2 cm

Pelvic lymphadenectomy

- Laparoscopic pelvic LND
- Sentinel Node
(immediate F/S or final pathology)



Abd.Trachelectomy in Baskent



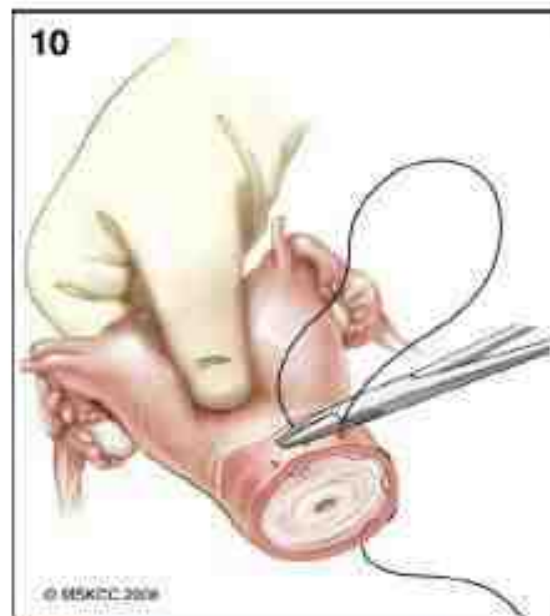
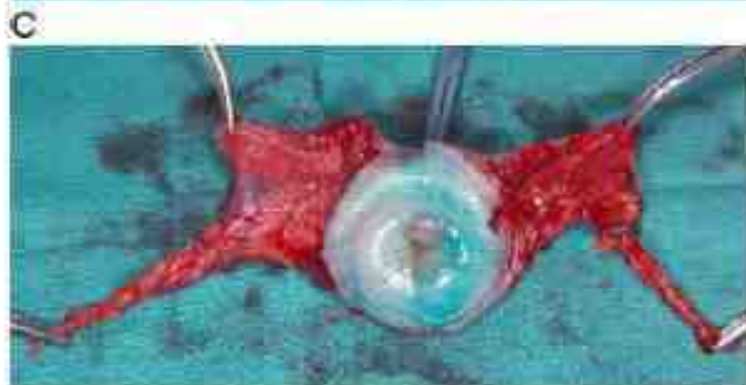
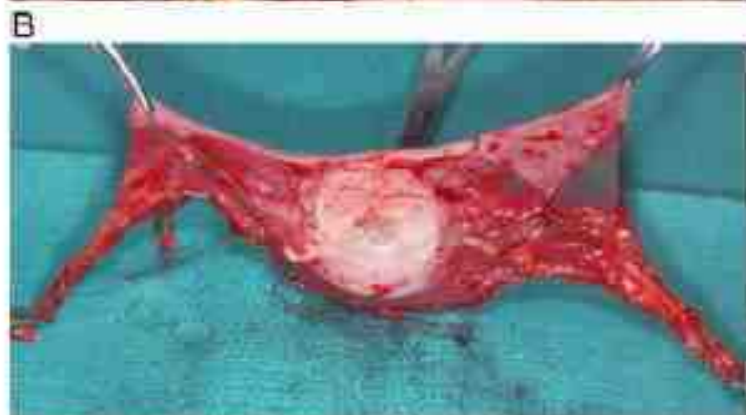


Fig. 10 and 11. A permanent cerclage with #0 Ethibond on a Ferguson needle is placed and the knot tied posteriorly.

Obstetric & Oncologic outcome - TRACHELECTOMY

	Patients	Pregnancies	Live Births	Recurrence	Death
Shepherd et al	123	55	28	5	4
Dargent et al	96	55	36	4	3
Burnett et al	21	3	2	0	0
Bernardini et al	80	22	18	7	4
Plante et al	72	50	36	2	1
Schlaerth et al	10	4	2	0	0
Schneider et al	36	7	4	1	0
Boss et al	19	2	2	0	0
Ungar et al	30	3	2	0	0
Mathevet et al	95	56	34	4	0
TOTAL	582	257(%44)	164(%64)	23(%3.9)	12(%0.2)

Fertility Sparing Treatment in Gynaecologic Cancers at Baskent University Hospitals

FSA	N Ptx / Married	Preg/Live birth	Recc	OAS mean(range)	Follow-up mean(range)
Cx Ca	22/7	4/1	3/22	34,79 (1 -80)	34,3 (1- 80)
End Ca/ EIN	37/32	10/11	7/37	38,4(8-97)	38,4 (8-97)
EOC	27/15	4/5	7/27	35,9 (6-149) 4 exitus	42,52 (6 - 142)
Non-EOC	35/20	10/10	4/35	45,8 (4 -219) 2 exitus	43,2 (4-145)
BOT	41/31	14/14	14/41	59,44 (5-175)	59,44(5-175)
Sarcoma	11/10	3/3	9/11	48,7 (16-97) 3 exitus	48,73 (16 - 97)
Total	173/115	45/44	44/173	9/173 ex	

Delivery After Any Cancer Treatment

	n	%
❖ End Ca	6	15,3
❖ Ovarian Ca*	20	51,3
❖ Breast Ca	5	12,8
❖ GTN	2	5,1
❖ Cx Ca	1	2,5
❖ Opere Pecoma	1	2,5
❖ Vulvar Sarcoma	3	7,5
❖ Lymphoma	1	2,5
❖ Total	39	100,0

*BOT, GCT, EOC

37 GYN

2 Non-GYN

38 C/S

Mean birth w.

2850gr

Conclusions

Advances in Treatment modalities

Prolonged Survival, QoL

**More Survivors and Fertility
Desire**

- Patient **Concent**
- **Selected patients**
- **Expected high survival**
- Similar oncologic outcome
- **Limited retrospective studies**
- **Experienced team (oncofertility teams)**
- Close follow up



***Thank you for your
attention***



TÜRK

JİNEKOLOJİK ONKOLOJİ DERNEĞİ