Surgical approaches for preserving fertility in cancer patients

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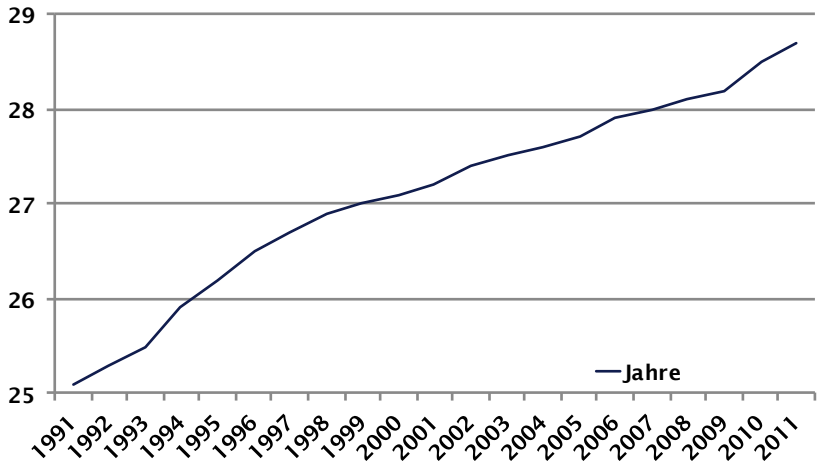
Topics

- Cervical cancer
  - Conization
  - (radical) trachelectomy
  - Neoadjuvant chemotherapy
- Ovarian cancer
  - Early stage disease
- Endometrial cancer
  - Ovarian preservation in early stage

Maternal age at 1st delivery



Statistik Austria, 2012.

Cervical Cancer

Cervical cancer + Fertility → 3 scenarios

- Very small tumor: conization
  - FIGO 1a1 + 1a2
  - Pelvic lymphadenectomy?
- Small tumor: (radical) trachelectomy
  - ≤FIGO 1b1 (ideal <2cm, max. 4cm diameter)
  - Always pelvic LNE/SNL before tumor surgery
  - Inner border: patient selection!
- Larger local tumor: NACT + surgery?
  - Selected patients
  - pelvicLNs → if negative, NACT → surgery

Cervical cancer: (very) early stage

- FIGO 1a1/1a2
  - Young pats, commonly incidental finding after conization

Survival in cervical cancer FIGO 1a after conization

Author	N	stage	DOD	Survival
Webb[1]	131	1a1	1 (0.8)	99.2%
	170	1a2	3 (1.8)	98.2%
Winter[1]	494	1a	4 (0.8)	99.2%
Rakar	237	1a	4 (1.7)	98.3%
Buckley[1]	94	1a2	4 (5.3)	94.7%
MUV[1]	86	1a	1 (1.2)	98.8%

[1]No case with parametrial involvement described

Prognostic factors and Management

Risk for LN metastasis

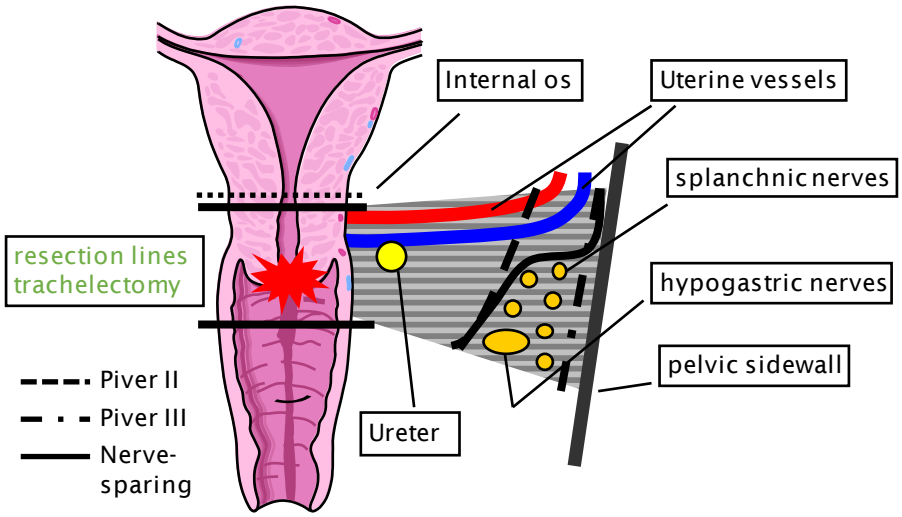
LVSI n=581	Stroma invasion <3mm	3.1-5mm
Negative (n=479)	0.8%	8.3%
Positive (n=102)	8.2%	7.5%

Ostor AG et al. 1995

Management

- FIGO 1a1 no LVSI: conization only
- FIGO 1a1 + LVSI: conization + pelvic LNE
- FIGO 1a2: always conization + pelvic LNE

Cervical cancer: early stage



ART: recurrence risk, patient selection

- Tumor size ≤2cm vs. >2cm – 1.6% vs. 29% recurrence rate
  (Marchiole et al., Gynecol Oncol 2007)
- LVSI (yes/no) – 12% vs. 2%
  (Marchiole et al., Gynecol Oncol 2007)
- 10-12% - endocervical tumor spread, LN-metastasis, parametrial involvement, positive margins
  (Marchiole et al., Gynecol Oncol 2007; Shepard et al., BJOG 2006; Beiner et al., Nat Clin Pract Oncol 2007)

Patient selection

Inclusion criteria

- squamous, Adeno(squamous)
- ≤ FIGO IB1 (better: <2cm)
- Pats desire for fertility
- No obvious hint for infertility
- MRI (endocervical margin)
- Fit for surgery
- Min. 4-6 weeks after LLETZ
- Age ≤ 45yrs.

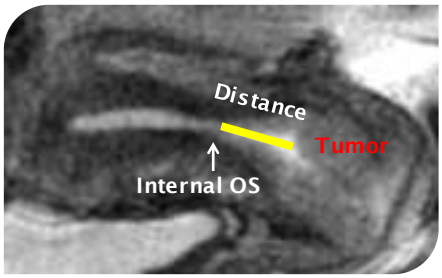
Diaz et al., Gynecol Oncol 2008.

Preoperative imaging

- MRI
  - Local spread (overestimation: clinical exam > CT > MRI)
  - Parametrial involvement (MRI > clinical exam) GOG 183
- PET-CT
  - LN: highest sensitivity and specificity (low FPR)
  - False negative rate for paraaortic LNs
    - 12% if pelvic LNs negative
    - 22% if pelvic LNs positive

Mitchell et al., JCO 2006; Hricak et al., 2005; Cormier et al., Gynecol Oncol 2011.; Gouy et al., Lancet 2012.

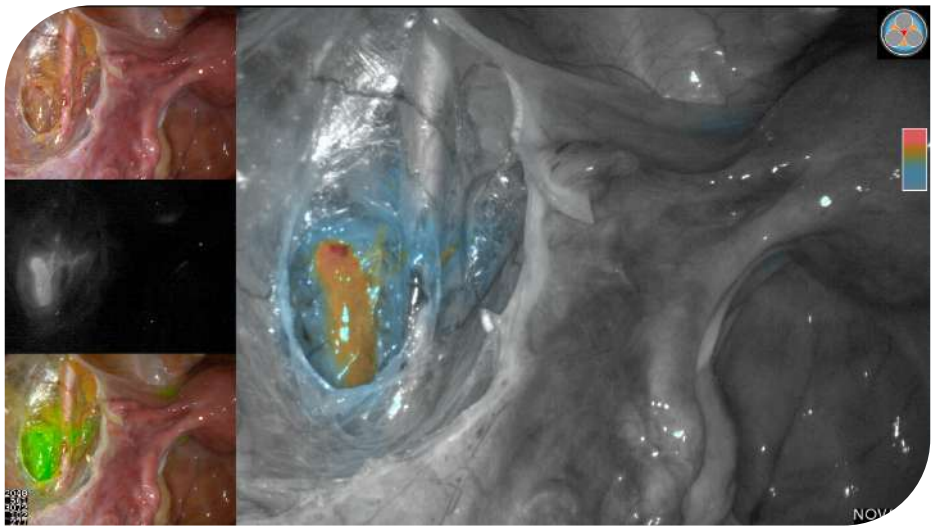
Preop imaging and surgical outcome



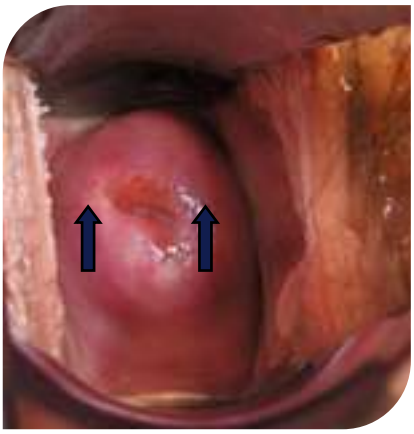
Distance: tumor → internal os	Surgical procedure Hysterectomy	trachelectomy	P
	N (%)	N (%)	
0-5mm	9 (100%)	0%	<.001
6-9mm	3 (60%)	2 (40%)	
≥10mm	3 (6%)	45 (94%)	

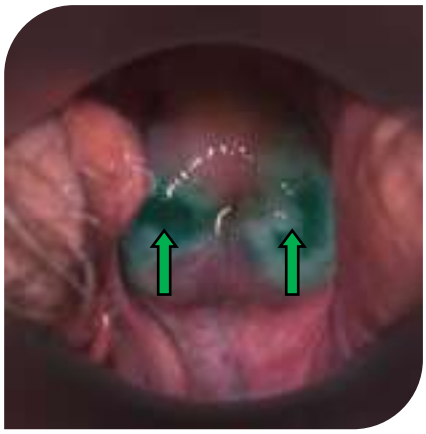
Lakhman et al., Radiology 2013.

LN-status: Sentinel lymph node



Indocyanine Green (ICG) - Sentinel lymph node





22G spinal needle : 3+9 o'clock (1cc superficial and 1cc deep each side)

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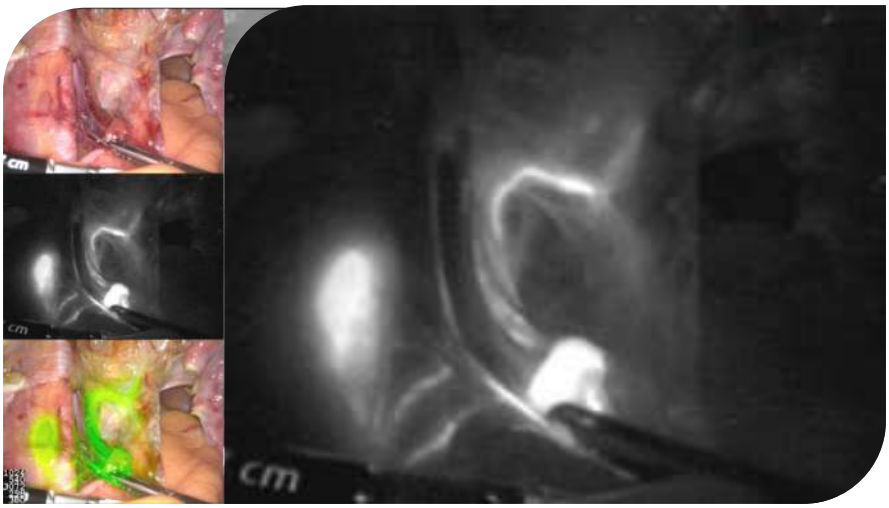
ICG-SNL (secondary lymph nodes)



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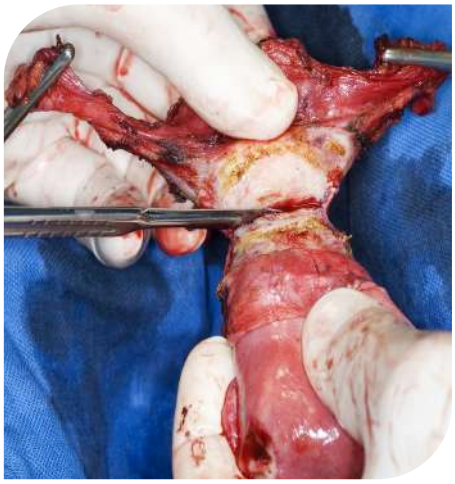
ART: surgical steps



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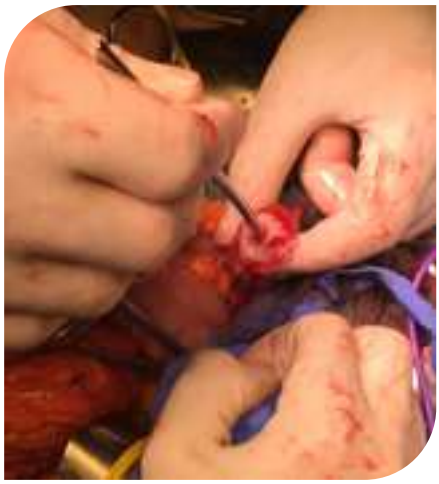

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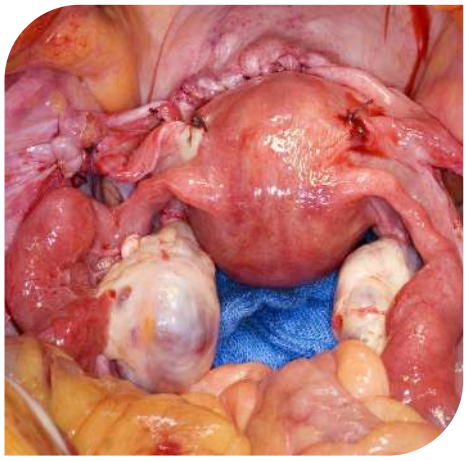
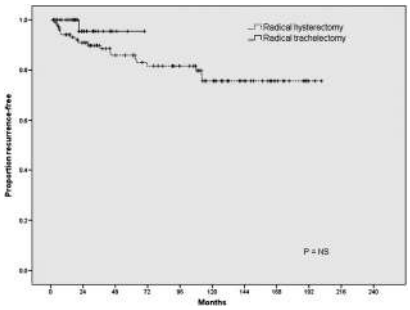


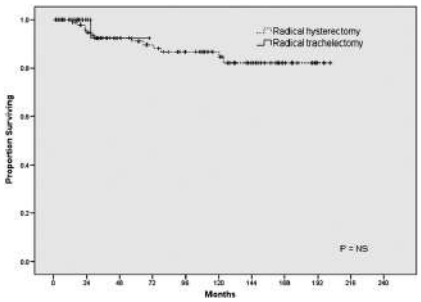
ART: optimal outcome

ART – oncologic outcome

Recurrence



Overall survival



- 5yr-recurrence free survival: RT 90% vs. RH 86%
- 5yr-overall survival: RT 92% vs. RH 91%
- Other treatment:
  - 5% conversion rate to RH, incl. FIGO 1b 15%
  - 5% adjuvant Radio(Chemo)therapy, incl. FIGO 1b 16%

Diaz et al., Gynecol Oncol 2008; Beiner and Covens, Nature Clin Pract Oncol 2007.

ART – pregnancy outcomes

- Attempted conception: 41-79%
- 88% pregnancy rate
  - 18% 1st trimester abortions
  - 44% live births >34th GW
  - 66% live births >34th GW

Diaz et al. Gynecol Oncol
Rob et al. Lancet Oncol

Diaz et al., Gynecol Oncol 2008; Rob et al., Lancet Oncol 2011.

NACT → Fertility-Sparing Surgery

Table 3. Neoadjuvant chemotherapy and fertility-sparing surgery

Study	Patients, *n*	Median age, y	Histotype	Stage	CT regimen	Type of treatment	Oncologic results DFS, %	OS, %	Obstetric results Pregnancies *n*	Live births, *n*
NACT + Conization										
Maneo et al. (2008) [90••]	21	30	9 SCC 12 Adk	21 IB1	9 TIP 12 TEP	LPS PLF + CON	100	100	10	9
Salihi et al. (2015) [93]	11	32	6 SCC 4 Adk 1 Adenosq	10 IB1 1 IB2	2 TIP 9 TC	LPS PLF + CON	100	100	6	7
NACT + Trachelectomy										
Marchiole et al. (2011) [94]	7	28	4 SCC 3 Adk	2 IB1 > 2 cm 3 IB2 2 IIA1	5 TIP 2 TEP	LPS PLF + VRT	100	100	1	0
Lanowska et al. (2014) [92]	20	32	11 SCC 8 Adk 1 Adenosq	14 IB1 > 2 cm 5 IB2 1 IIA	TIP	LPS PLF + VRT	95	100	7	4
Robova et al. (2014) [91]	28	29	15 SCC 13 Adk	21 IB1 7 IB2	IP (cisplatin–doxorubicin for Adk)	LPS PLF + ST	80	90	13	11
									43%	78%

Adenosq adenosquamous, *Adk* adenocarcinoma, *CON* conization, *CT* chemotherapy, *DFS* disease-free survival, *IP* ifosfamide, and cisplatin, *LPS* laparoscopic, *NA* not available, *NACT* neoadjuvant chemotherapy, *OS* overall survival, *PLF* pelvic lymphadenectomy, *SCC* squamous cell carcinoma, *SLN* sentinel lymph node mapping, *ST* simple trachelectomy, *TC* paclitaxel and carboplatin, *TEP* paclitaxel, epirubicin, and cisplatin, *TIP* paclitaxel, ifosfamide, and cisplatin, *VRT* vaginal radical trachelectomy

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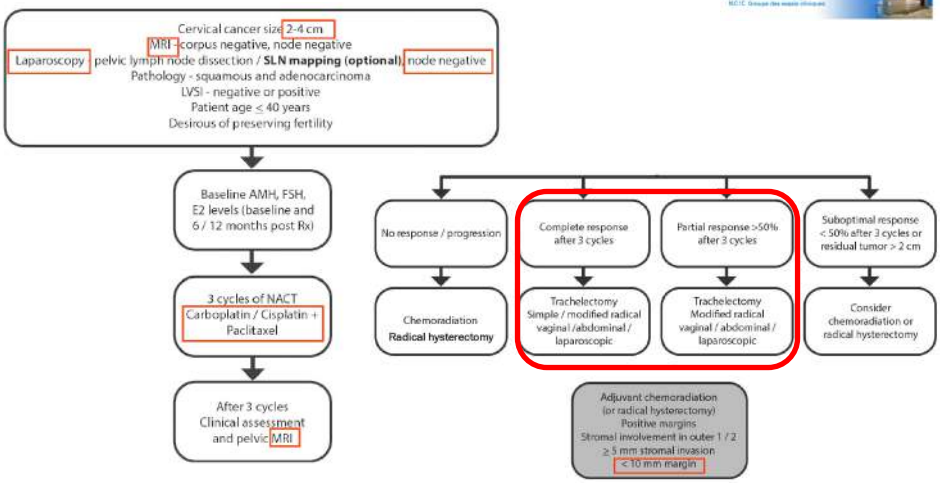
Tomao et al. Curr. Treat. Options in Oncol (2016)

Stage IB1 (2-4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility Sparing Surgery (CoNteSSA)

GYNECOLOGIC CANCER INTERGROUP

AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP



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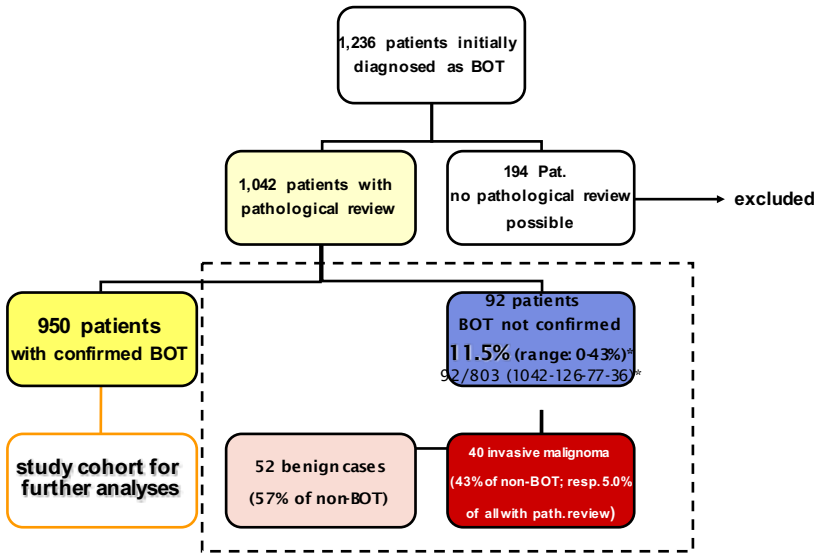
Ovarian Cancer

Ovarian cancer + Fertility → 2 scenarios

- Borderline tumor of the ovary (BTO)
  - Thourough Surgical staging
  - Pathologic review
- Early stage epithelial ovarian cancer (EOC)
  - Risk for upstaging is high!
  - If "understaged" pat might not receive chemo → recurrence

BTO: pathology is key!

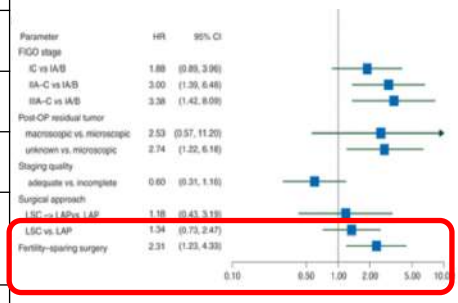


ROBOT: prognostic factors - univariate

Factor		HR	95%CI	N	E	logrank p
Stage	FIGO I	1.000	-	782	72	**<0.0001**
	FIGO II/III	2.486	1.663 - 3.715	168	36	
Microinvasion	w/o microinvasion	1.000	-	901	99	0.1087
	with microinvasion	1.737	0.877-3.439	49	9	
surgical access	laparotomy (incl. conversions)	1.000	-	652	75	0.4976
	laparoscopy	1.154	0.763 - 1.744	297	33	
Post-OP residual tumor (61 pts. with missing data excluded)	w/o macroscopic residuals	1.000	-	877	90	**<0.0001**
	with macroscopic residuals	4.905	2.144-11.221	12	6	
Staging quality	adequate	1.000	-	390	29	**0.0082**
	incomplete	1.765	1.152 - 2.706	560	79	
Re-staging surgery (720 pts with initial incomplete staging)	w/o re-staging surgery	1.000	-	401	63	**0.0198**
	with re-staging surgery	0.577	0.362 - 0.922	319	25	
Fertility preservation OP	no	1.000	-	782	68	**<0.0001**
	yes	2.979	2.013 - 4.409	168	40	
Organ preservation surgery (2 pts with missing data exduded)	bilateral salpingo-oophorectomy	1.000	-	708	63	**<0.0001**
	unilateral salpingo-oophorectomy	1.713	1.108 - 2.649	199	30	
	cystectomy	5.662	3.154-10.166	41	14	

ROBOT: prognostic factors - multivariate

Factor	HR	95% CI	p
Post-OP Residual tumor	4.980	(2.131, 11.640)	0.0002
Implants present yes/no	2.743	(1.675; 4.494)	<0.0001
Organ preservation	2.363	(1.226; 4.554)	0.0102
Staging quality adequate vs. incomplete	2.188	(1.315; 3.683)	0.0026
Age [years]	0.838	(0.726; 0.968)	0.0166



- Fertility sparing surgery seems feasible in BTO patients
- Careful staging (omentectomy, peritoneal biopsies, check for implants)
- 2-fold risk for recurrence (19% vs 10% 5yr RR)
- Some guidelines: completion surgery after family planning finished

Early stage ovarian cancer

Facts

- FIGO 1 rare in OC: 20%
- quality of surgical staging is prognostic
  - Pelvic + paraaortic LN staging
  - Exclude peritoneal disease
- understaging 16-60%!!
  - Macroscopic residuals (prognostic)
  - No chemo! (prognostic)

Stage/grade	n	Recurrence
IA, grade 1	300	18 (6.0%)
IA, grade 2	80	10 (12.5%)
IA, grade 3	37	14 (37.8%)
IC, grade 1	139	12 (8.6%)
IC, grade 2	44	5 (11.4%)
IC, grade 3	24	6 (25.0%)

- Risk of recurrence in OC > FIGO IA-IC g1: 11-33%
  - May be offered in pts with FIGO IA-IC g1
  - Caution in g2-tumors → individual decision
  - Not recommended in g3 or > FIGO I
- FSS can not be recommended as routine clinical surgery

FSS in early OC: pregnancy outcome

Reference	Patients	Pregnancies		Live births at term within the observation period[a], n
		Patients who became pregnant, n (%)	Total number of pregnancies, n	
Raspagliesi et al. 1997 [19]	10	3 (30.0%)	3	2
Zanetta et al. 1997 [13]	56	20 (35.7%)	27	17
Schilder et al. 2002 [20]	52	17 (32.7%)	32	26
Colombo et al. 2005 [21]	24	6 (25.0%)	7	6
Morice et al. 2005 [22]	34	9 (26.5%)	10	6
Borgfeldt et al. 2007 [16]	11	7 (63.6%)	14[b]	14
Park et al. 2008 [23]	62	15 (24.2%)	24	22
Anchezar et al. 2009 [24]	18	6 (33.3%)	7[b]	7
Kwon et al. 2009 [25]	21	5 (23.8%)	5[b]	5
Schlaerth et al. 2009 [26]	20	6 (30.0%)	9[b]	9
Kajiyama et al. 2010 [27]	60	9 (15.0%)	13	9[c]
Satoh et al. 2010 [12]	211	55 (28.5%)	76	66
Hu et al. 2011 [28]	94	12 (12.8%)	17	7[d]
Fruscio et al. 2013 [29]	240	84 (35.0%)	108[b]	92
Sum	913	254	352[b]	288

28% 82%

[a]Reliable assignment to the pertinent patient (regarding the number of children per patient and/or correlation of fertility outcome with prognostic criteria) is not possible.
[b]Minimum number of pregnancies according to published information.
[c]Plus 1 additional preterm delivery after ≤ 35 weeks of pregnancy.
[d]Plus 2 ongoing pregnancies at time of assessment.

du Bois et al., Onkologie 2013

Endometrial Cancer

Early stage EC: ovarian conservation

Facts

- Risk for synchronous/ metachronous OC: 5%
- OC mets higher younger pats (genetics)
- BSO → early menopause
  - ↑ Cardiovascular disease
  - ↑ osteoporosis
  - ↑ Metabolic syndrome

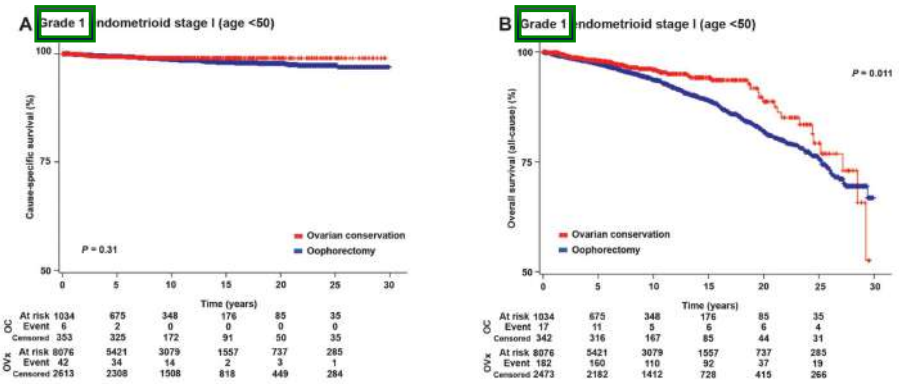
Eligibility criteria

- Endometrioid EC, FIGO 1A, g1/2
- Age ≤ 50yrs.
- No adnexal mass (TVUS/MRI)
- No hereditary syndrome (Lynch syndrome, BRCAm)
- BS performed anyway

Soliman PT, Gynecol Oncol 2004, Song T, Int J Gynecol Cancer 2014, Williams MG, Obs Gynl 2009; Ward KK, Gyn Onc 2012

Ovarian conservation in young women

- 1242 patients EC FIGO I ovarian conservation < 50 years
- 12860 (9.7%) patients EC FIGO I BSO < 50 years
- SEER database, univariate & multivariate analyses



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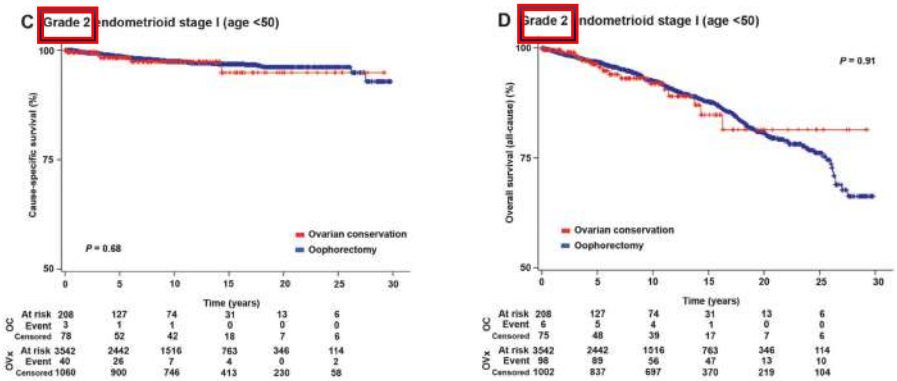
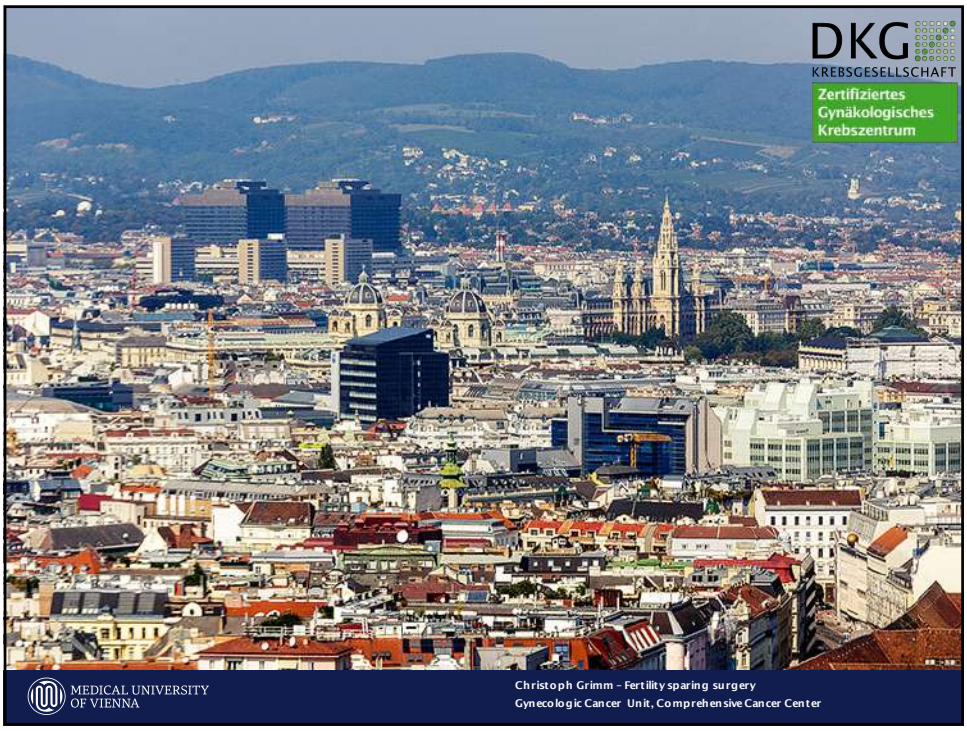


Matsuo K, Obstet Gynecol 2016

Summary

- Cervical cancer
  - LN evaluation
  - <2cm FSS, >2cm (NACT → surgery)
  - Pregnancy: 40-80% attempt conception; 44-66% live birth rate
- Ovarian cancer
  - Only FIGO I, grade is crucial
  - Risk for understaging (tumor residuals, chemo)
  - Pregnancy: 30% attempt conception; 80% live birth rate
- Endometrial cancer
  - Ovarian preservation feasible in FIGO I



Therapie der EH

- Entscheidungsfindung
  - EH +/-Atypie
  - Symptomatik
  - Kinderwunsch
- Therapieoptionen
  - Megestrolacetat 40-200mg/d (USA)
  - Medroxyprogesteronacetat (MPA)
    - Kont.: MPA 100-600mg/d
    - Zyklisch: MPA 10-20mg/d für ZT_{12-25}
  - Levonorgestrel-IUD (Mirena) 20mcg/d
    - Höchste Effektivität? Orbo et al., Gynecol Oncol 2008

Reed et al., Obstet Gynecol. 2009; Trimble et al., Obstet Gynecol 2012; Orbo et al., Gynecol Oncol 2008

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(Fertilitätserhalt) – state of the art?

- Rationale – EC: 15% prämenopausal, 5% <40 Lebensjahr
- Voraussetzung
  - Alter <45 LJ, Kinderwunsch
  - Endometrioides AdenoCA, G1
  - Bildgebung: keine MI, kein Hinweis auf extrauterine Ausbreitung
- Therapie
  - Medroxprogesteronacetat (MPA) 200-600mg/d
  - Levonorgestrel IUD (Mirena©)
  - Megestrolacetat 40-160mg/d (USA)

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Fertilitätserhalt – state of the art ➔ NEIN

- Outcome (55% retrospektive, 45% prospektive Kohorten)
  - Regressionsrate 76.2%
  - Lebengeburtenrate 28%
  - Progressionsrate 1.8% (FIGO II+)
  - Rezidivrate 40.6%
  - Mittlere Rezidivdauer 24 Monate
  - OvarialCA/ovarielle Metastase des EC: 3.8%
- Nachsorge
  - Vag. Sono, HSK/Curettage alle 3 Monate für 1 Jahr, danach q6m
  - Komplettierung durch HE/Adnexektomie bil nach Abschluss der Familienplanung

Gallos et al., Am J Obstet Gynecol 2012; Gunderson et al., Gynecol Oncol 2012; Baker et al., Gynecol Oncol 2012

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Schwangerschaftsoutcome

- Metaanalyse von 14 Studien EH mit Atypien
  - 31/126 Frauen mit Lebendgeburt
  - Lebendgeburtrate: 26.3% (95%KI: 18-37%)
  - IVF vs spontan?
    - IVF: 39.4% Lebendgeburtrate
    - Spontan: 14.9% Lebendgeburtrate
- CAVEATS
  - Bias: besseres FU bei IVF!
  - Rezidivrate: 26% (95% KI: 18-37%)
  - Mittlere Rezidivdauer: 32 Monaten

Gallos et al., Am J Obstet Gynecol 2012

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Wiederholungstherapie

- Rezidivtherapie nach Gestagen
  - aEH und EC
  - MPA (80 bzw 500mg/d) n=30, MA (80 bzw. 160mg/d) n=3
  - Med. Dauer: 6 Monate
- Ansprechen
  - 28/33 (85%) CR
  - 5 Rezidive

Park et al., Obstet Gynecol 2013

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