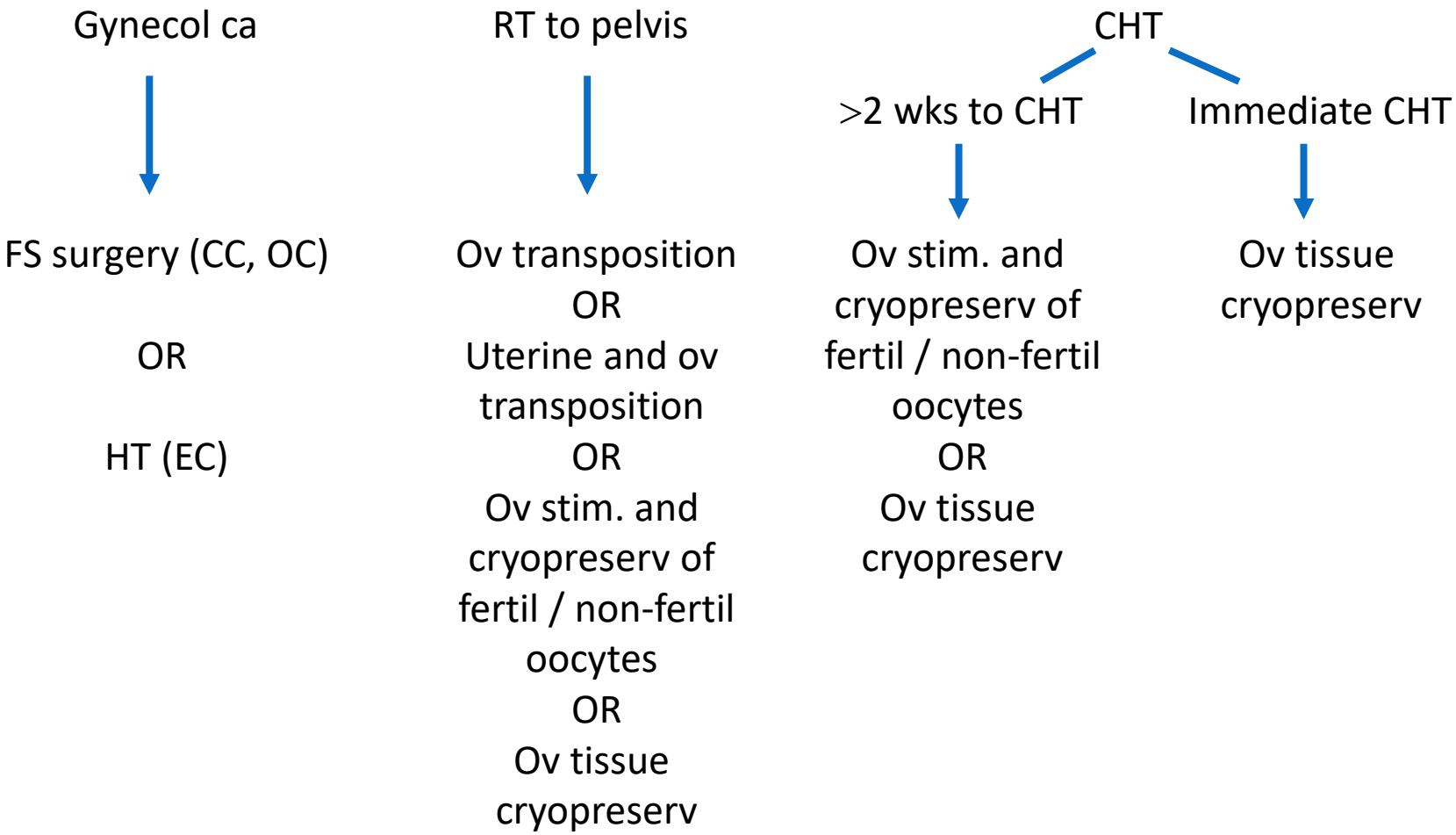
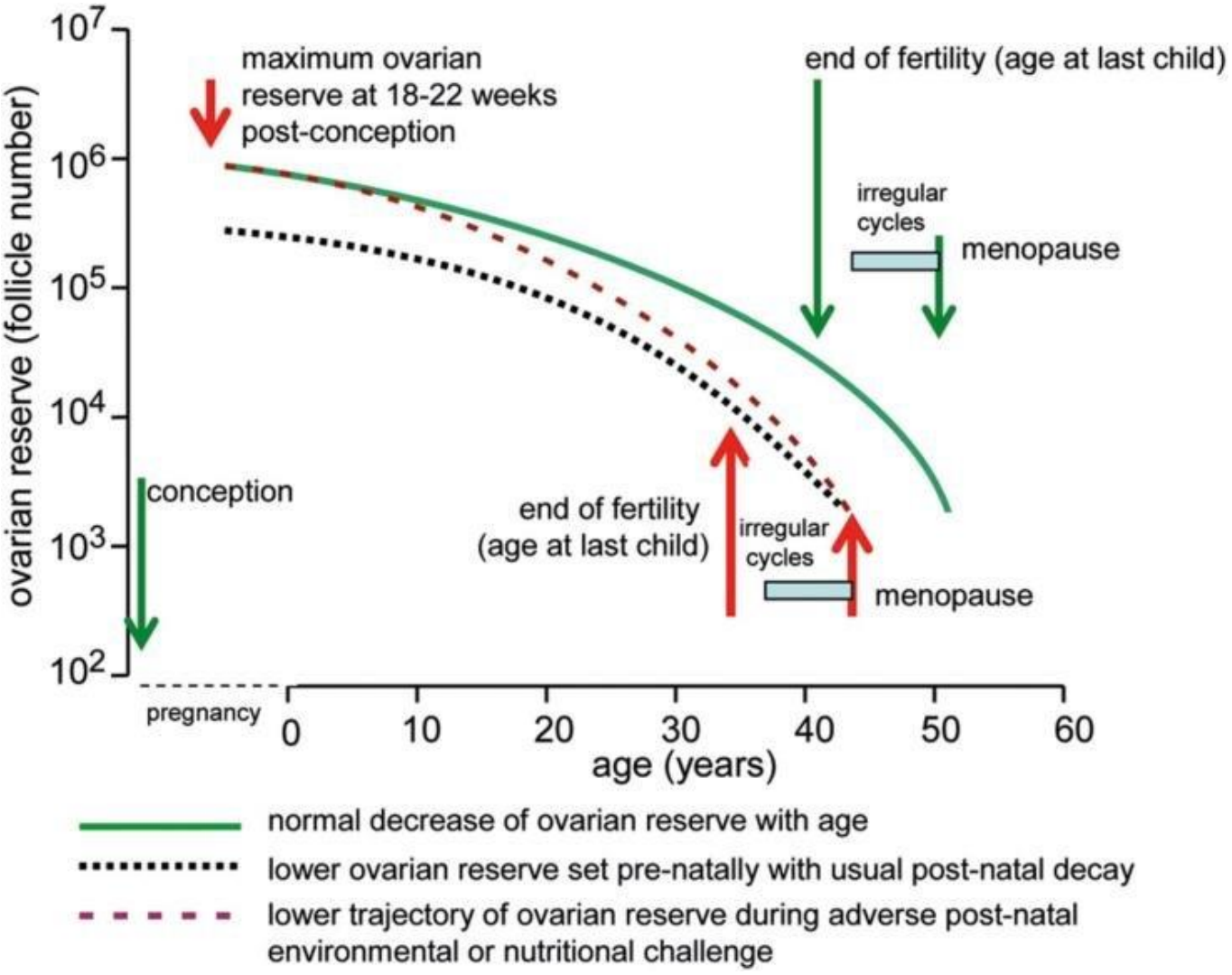
Fertility preservation ALG



Možnosti ochrany reprodukčních funkcí během pánevní radioterapie

David Cibula

Onkogynekologické centrum
Gynekologicko-porodnická klinika VFN a 1. LF UK


ovarian reserve (follicle number)
10^7
10^6
10^5
10^4
10^3
10^2
maximum ovarian reserve at 18-22 weeks post-conception
end of fertility (age at last child)
irregular cycles
menopause
conception
end of fertility (age at last child)
irregular cycles
menopause
pregnancy
0
10
20
30
40
50
60
age (years)
normal decrease of ovarian reserve with age
lower ovarian reserve set pre-natally with usual post-natal decay
lower trajectory of ovarian reserve during adverse post-natal environmental or nutritional challenge

Ovarian function

≤ 2 Gy	destruction of 50% of oocytes
4 Gy	POF in 1/3 < 35 years
	POF in all > 40 years
10 Gy	POF in 100%

Ovarian function preservation

Ovarian stimulation and cryo-preservation

- oocytes / embryos

Ovarian tissue cryo-preservation and transplantation

- orthotopic
- heterotopic (1st live birth 2004; 18 babies)

Ovarian transposition

Ovarian transposition

Review

1130 studies $\rightarrow$ 38 eligible $\rightarrow$ 765 patients only

Conclusion:

ovarian function after OT is successful in 20 – 100%

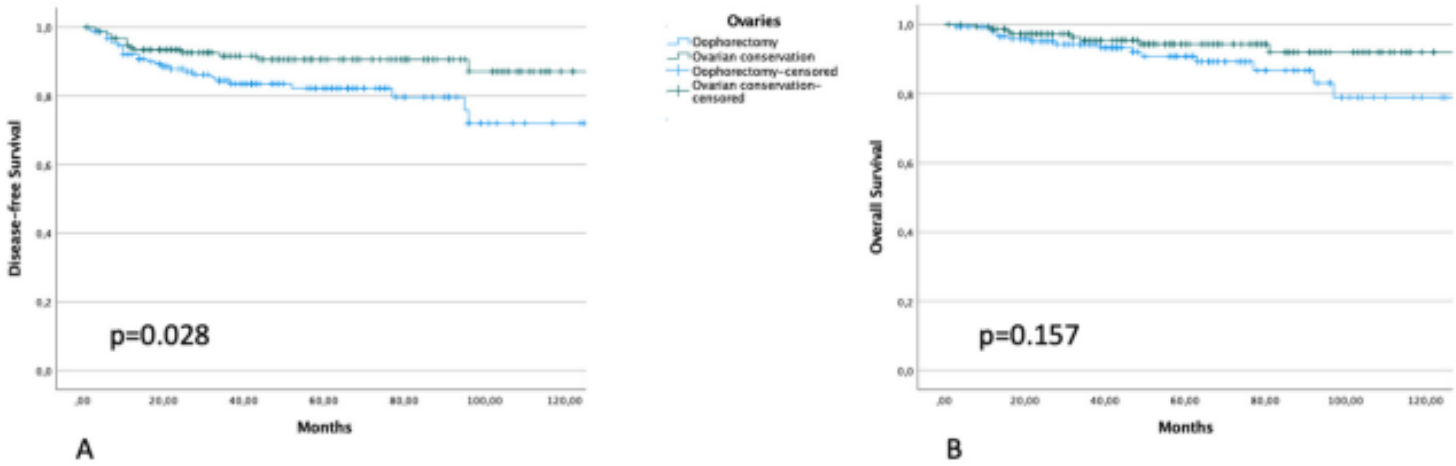
Eur J Surg Oncol 2019, 45, 1328-1340

Ovarian preservation in cervical cancer

Retrospective multicenter study

Stage IA1-IIA1; 2007 – 2019

Ovarian site recurrence N=2 (1.3%)



Int J Gynecol Cancer, 2021, 47, 2158-2165

Ovarian transposition in cervical cancer

OT in cervical cancer

635 studies $\rightarrow$ 33 eligible $\rightarrow$ 1377 patients

Conclusion:

ovarian function preservation	62%
ovarian metastases	0.4%
peri-operative complications	8.5%

Int J Gynecol Cancer, 2021, 31, 360-70

Ovarian transposition

A prospective study

N=104 pelvic ca

Prevention of POF

90% after BRT

60% after EBRT

Complications

Pain

Injury to ovarian vessels

Torsion

Inflammation

JMIG, 24, 2011

Ovarian transposition

Cervical cancer patients, single institution

Ovarian transposition: 53/414

2002 – 2010; NCI South Korea

Ovarian function preservation:

FSH $<$ 30 + no menopausal symptoms

Conclusions:

ovarian function preservation after adjuvant RT only 32%

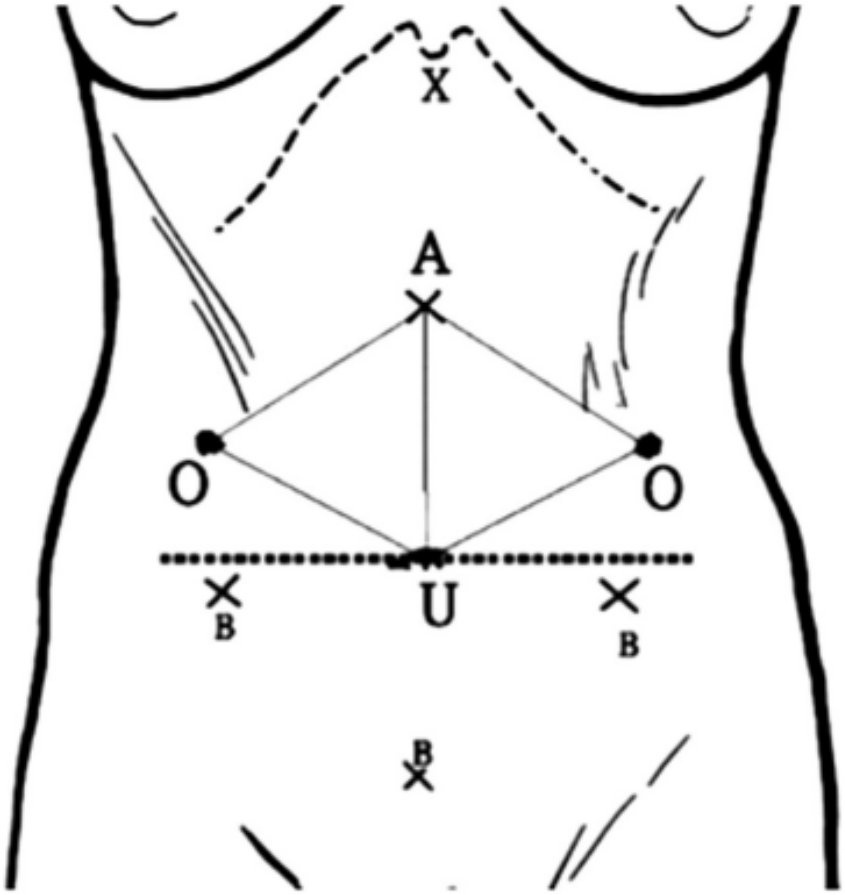
location of transposed ovary the most important factor for ovarian function preservation (OR 11.72)

(1.5 cm above the iliac crest

Fert Steril, 2012, 97, 1387-93

Fig. 2

Trocar placement strategy. O: Final destination of the ovaries; A: Subxiphoid optical trocar site (Lee-Huang point); U: Umbilicus; B: Accessory trocar sites. Graph reprinted from Reference [24], with permission from Elsevier.



Moawad NS: JMIG, 24, 2017.

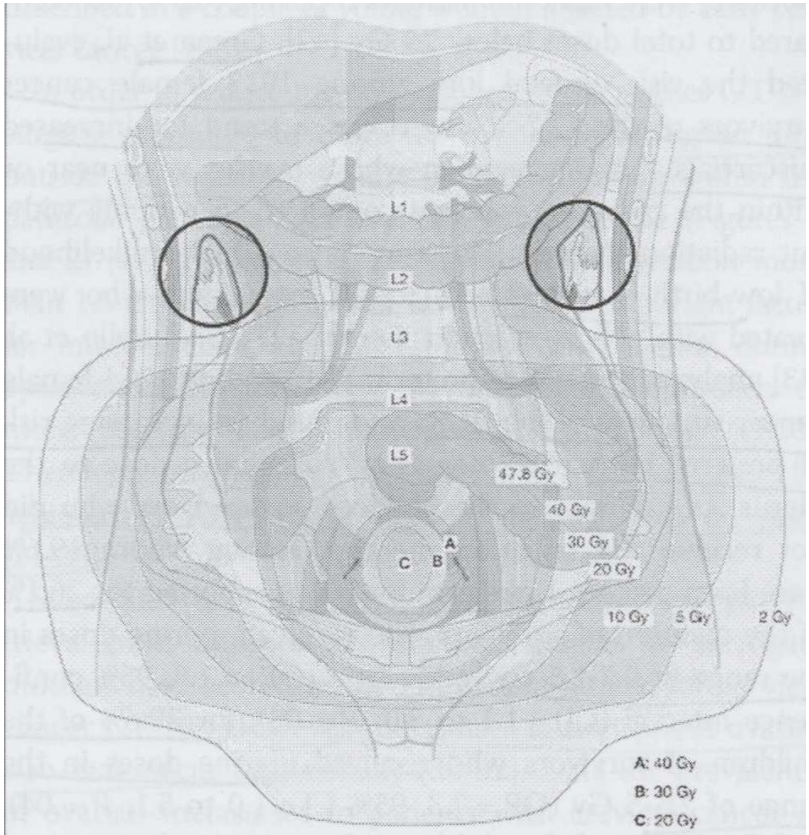


Figure 3 Isodoses of the prescribed dose (47.8 Gy) in the target volume decreasing to the periphery and to the ovaries (in black circles) to < 2 Gy between second (L2) and third (L3) lumbar vertebrar. Selective dose reduction within the intact uterus from 40 Gy **(A)** to 30 Gy **(B)** in the periphery to 20 Gy **(C)** in the inner layer of the myometrium and endometrium.

Rad Oncology 2015, 10.

Radiotherapy and Oncology xxx (2018) xxx–xxx

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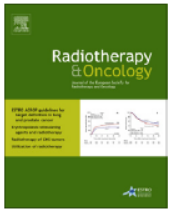


Original article

The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer

David Cibula [a,*], Richard Pötter [b], François Planchamp [c], Elisabeth Avall-Lundqvist [d], Daniela Fischerova [a], Christine Haie Meder [e], Christhardt Köhler [f], Fabio Landoni [g], Sigurd Lax [h], Jacob Christian Lindegaard [i], Umesh Mahantshetty [j], Patrice Mathevet [k], W. Glenn McCluggage [l], Mary McCormack [m], Raj Naik [n], Remi Nout [o], Sandro Pignata [p], Jordi Ponce [q], Denis Querleu [c], Francesco Raspagliesi [r], Alexandros Rodolakis [s], Karl Tamussino [t], Pauline Wimberger [u], Maria Rosaria Raspollini [v]

Ovarian preservation should be offered to premenopausal patients with squamous cell carcinoma and usual-type (human papillomavirus [HPV] related) adenocarcinoma.
Bilateral salpingectomy should be considered.

Ovarian preservation in EC

Risk of adnexal involvement
788 patients with endometrial cancer and normal adnexa on clinical staging

Univariační analýza

Variable	Adnexal involvement (No. of patients)			
	Category	Absence	Presence	*p*
Age	< 45 years	41	4 (8.9%)	0.13
	≥ 45 years	712	31 (4.2%)	
Histologic type	Endometrioid	656	21 (3.1%)	< 0.001
	Non-endometrioid	97	14 (12.6%)	
LVSI[a]	No	521	13 (2.4%)	< 0.001
	Yes	121	20 (14.2%)	
Myometrial invasion	< 50%	495	18 (3.5%)	< 0.001
	≥ 50%	257	31 (10.8%)	
Lymph node metastasis	No	522	14 (2.6%)	< 0.001
	Yes	83	17 (17.0%)	
Histologic grade	Grades 1 + 2	516	11 (2.1%)	< 0.001
	Grade 3[b]	232	24 (9.4%)	

[a]*LVSI* lymphovascular space invasion

[b]Includes endometrioid G3, and non-endometrioid histologies

No patient with clinically normal ovaries, age under 45, endometroid ca, stage I or II, Superficial myometrial invasion, N0 had adnexal involvement

Ann Surg Oncol, 2020, 27, 2822-2826

Ovarian preservation in EC

Review
Endometrial cancer stage I/II
7 studies → 1419 patients (preservation) vs 15.826 (BSO)

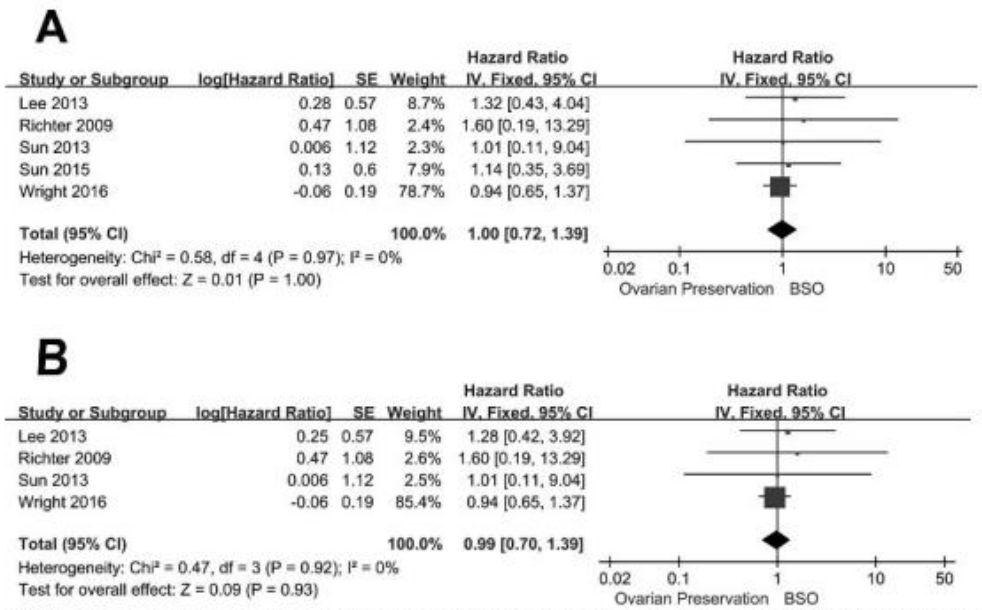


FIGURE 2. Comparison of OS between ovarian preservation and BSO group in EC patients: (A) all patients and (B) young and premenopausal patients.

J Int Med Res, 2019, 47, 2492-98

Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Recommendations

- Ovarian preservation can be considered in pre-menopausal patients aged <45 years with low-grade endometrioid endometrial carcinoma with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease (IV, A).
- In cases of ovarian preservation, salpingectomy is recommended (IV, B).
- Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (eg, *BRCA* mutation, Lynch syndrome, etc) (IV, B).

IJGC 2021, 31, 12-39

Ovarian preservation in LG ESS

LG ESS stage I

Ovarian preservation (N=202) vs BSO (N=541)

National Cancer Database, US

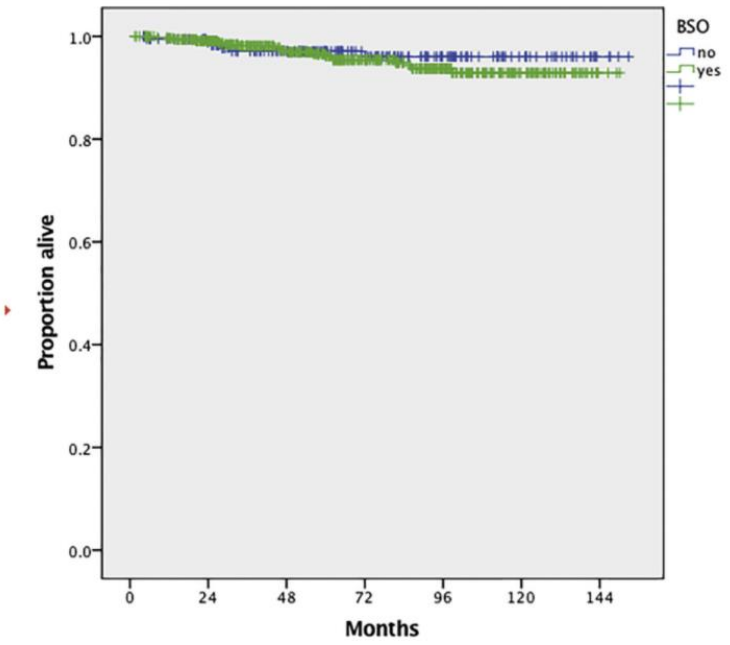


Fig. 1. Overall survival of premenopausal patients with stage I LG-ESS who did and did not undergo BSO.

GO 2020, 157, 634-638

Ovarian preservation in LG ESS

Review, 2019

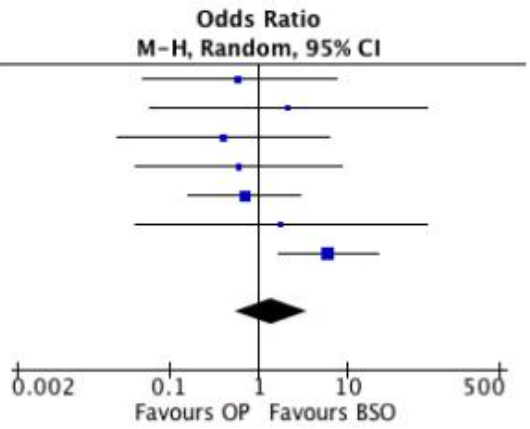
17 studies → 190 patients (vs 501 BSO)

RR increased	OR 2.7 (1.39-5.28)
PFS in premenopausal w. not different	OR 1.38 (0.55-3.5)
OS not different	OR 0.8 (0.18-3.47)

	Ovarian preservation		BSO			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Amant et al, 2007	1	6	3	12	11.5%	0.60 [0.05, 7.41]
Evans et al, 1982	1	4	0	2	6.1%	2.14 [0.06, 77.54]
Gaducci et al, 1996	1	6	2	6	10.0%	0.40 [0.03, 6.18]
Huang et al, 1996	1	6	2	8	10.3%	0.60 [0.04, 8.73]
Li et al, 2005	4	12	10	24	26.4%	0.70 [0.16, 2.98]
Mansi et al, 1990	1	3	0	1	5.6%	1.80 [0.04, 79.42]
Yoon et al, 2013	20	54	3	34	30.0%	6.08 [1.64, 22.47]
Total (95% CI)		**91**		**87**	**100.0%**	**1.38 [0.55, 3.50]**
Total events	29		20			

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 7.44$, df = 6 (P = 0.28); $I^2 = 19\%$

Test for overall effect: Z = 0.69 (P = 0.49)



Int J Gynecol Cancer, 2019, 29, 126-32

Uterus

Radiosensitivity ↓ with the age

- ↑ LBW babies
- ↑ Premature deliveries
- ↑ Fetal loss
- ↑ Miscarriages

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2021 Mar; 165(1):99-101.

Radiotherapy dose limit for uterus fertility sparing in curative chemoradiotherapy for rectal cancer

Radka Lohynska[a], Michaela Jirkovska[b], Alena Novakova-Jiresova[a], Eva Mazana[a], Kamil Vambersky[c], Tomas Veselsky[c], Anna Kindlova[c], Hana Stankusova[b], Bela Malinova[b]

Aims. Curative sphincter sparing radiotherapy is a treatment option for early rectal cancer. There are many methods developed for fertility preservation in young patients treated with pelvic radiotherapy. Pregnancy rates after radiotherapy are dependent on the radiation dose to ovaries and uterus. Data on outcomes of total body irradiation suggest a pregnancy is possible following 12-14 Gy TBI, despite elevated rates of preterm deliveries and other complications.
Methods. We report a case of full-term delivery of twins after curative chemoradiotherapy for anorectal adenocarcinoma T2 N0 M0 with the total dose 58.6 Gy. The patient underwent laparoscopic laterocranial ovarian transposition before radiotherapy.
Results. Long term complete remission was achieved after treatment. Although a spontaneous conception was not successful, the patient underwent an in vitro fertilisation procedure with donor eggs and conceived twins 10 years after the radiotherapy treatment. The mean dose to the uterus was 16 Gy and to the uterine cervix 35 Gy. She reached a full-term pregnancy and delivered two healthy babies by caesarean section at a gestational age of 38 weeks, weighing 2420 g and 2220 g.
Conclusion. This is the first case report of the successful pregnancy following sphincter sparing curative pelvic radiotherapy for rectal cancer. Furthermore it allows us to propose an increased limit dose to the uterus enabling fertility sparing beyond the limits achieved from total body irradiation series with 12-14 Gy and accept 16 Gy as uterine body (35 Gy for uterine cervix) limit for IMRT treatment planning in young patients asking for maintaining fertility potential.

Uterine preservation

Uterine transplantation

Uterine ventral fixation

Uterine sparing radiation therapy

Uterine transposition

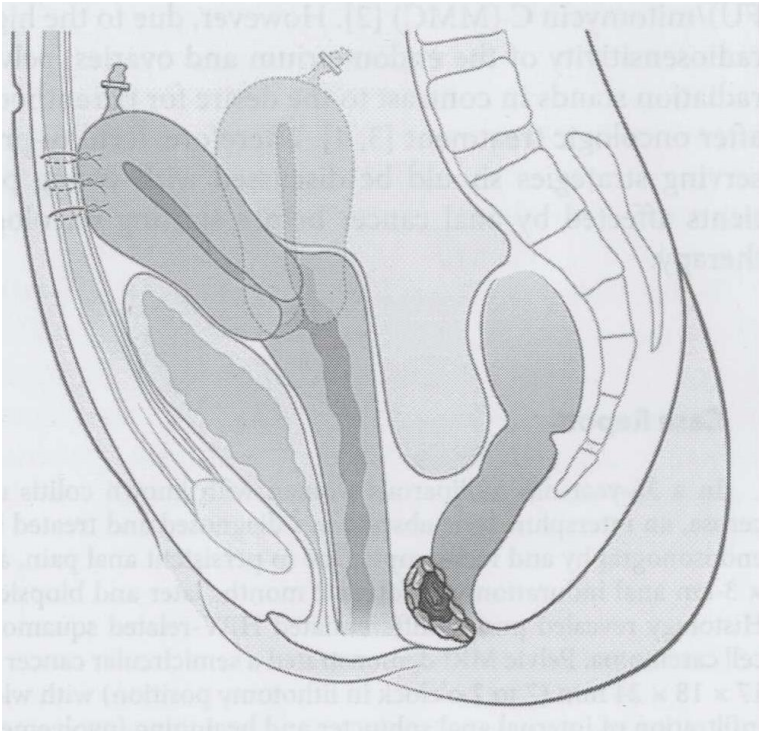
Uterine ventral fixation

36 y

Squamous anal cancer cT2 N0 G3 M0

Ovarian transposition

Uterus ventral fixation



Oncology 2016, 91, 295-98

Uterine ventral fixation

Primary CRT

IMRT – comb dose to tumor 59 Gy; Chemo 5FU

Recurrence after 6 mo

Rectoanal resection / stoma

After 2 years

IVF – antGnRH

LSC oocyte retrieval; ET of 2 embryos

Pregnancy / SC at 37 wk

Oncology 2016, 91, 295-98

Uterine preservation

Uterine transplantation

Uterine ventral fixation

Uterine sparing radiation therapy

Uterine transposition

Cyberknife robotic radiosurgery

cervical cancer

sparing dose to uterus

total dose of 90 Gy

experimental approach

Marnitz at al: Radiat Oncol 2013, 8, 109

Uterine preservation

Uterine transplantation

Uterine ventral fixation

Uterine sparing radiation therapy

Uterine transposition

Transpozice ovárií

premenopausální ženy $<$ 45 let

riziko komplikací $\sim$ 2-10%

zachování ovariální funkce 20 – 100%

klíčová je lokalizace dostatečně kraniálně

doporučena u časných stádií:

- karcinomu děložního hrdla
- stádia I-II (LR) karcinomu endometria
- LG ESS (?)
- karcinomu rekta (?)