

Fertility-sparing surgery in young patients with cervical cancer

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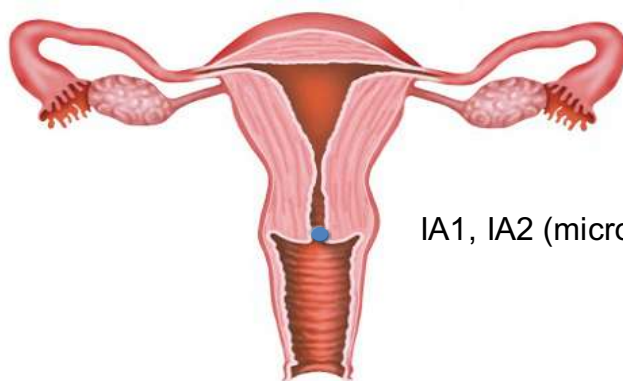
La pitié Salpêtrière

Evaluation BEFORE surgery

- Cancer: stage, type
- Patient's age
- Desire for future pregnancy
- Imaging+++
- Tumor Board, multidisciplinary decision (oncofertility network)
- Early specific oncofertility consultation

Key elements to stage

- Size (volume ?)
- Nodes
- Histology
- Lympho-vascular space involvement (LVSI)
- Clinical examination
- +/- Pathological review
- MRI
- PET CT for advanced stage



IA1, IA2 (microscopic): **conization**

Conization

Obstetrical risks (metanalysis Kirgiou Lancet 2006)

Obstetrical risks	Odd ratio (OR, IC 95%)
Preterm delivery	2.59 (1.80-3.72)
Premature rupture of the membranes	2.69 (1.62-4.46)
Caesarean section	3.17 (1.07-9.40)
Low birth weight (<2500g)	2.53 (1.19-5.36)

Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia (Review)



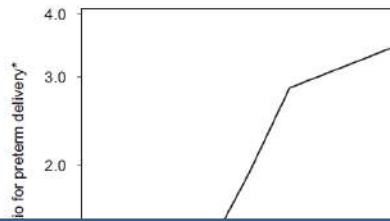
Cochrane Database of Systematic Reviews

Kyrgiou M, Mitra A, Arbyn M, Paraskevaidi M, Athanasiou A, Martin-Hirsch PPL, Bennett P, Paraskevaidis E 2015

Early pregnancy outcomes for cervical intraepithelial lesions

Patient or population: patients with cervical intraepithelial lesions
Settings: colposcopy clinics
Intervention: cervical treatment for CIN (excisional or ablative)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Untreated	Cervical treatment for CIN (excisional or ablative)				
2nd trimester miscarriage rates	Study population		RR 2.6 (1.45 to 4.87)	2182268 (8 studies)	⊕⊕○○ low^a	Observational studies only 5 studies assessed as low quality. 2 studies downgraded to very low quality due to study design (high risk of publication bias) and wide confidence intervals 1 study upgraded to moderate quality due to large study population and magnitude of effect
	4 per 1000	10 per 1000 (6 to 16)				
	Control population					
	11 per 1000	29 per 1000 (16 to 51)				

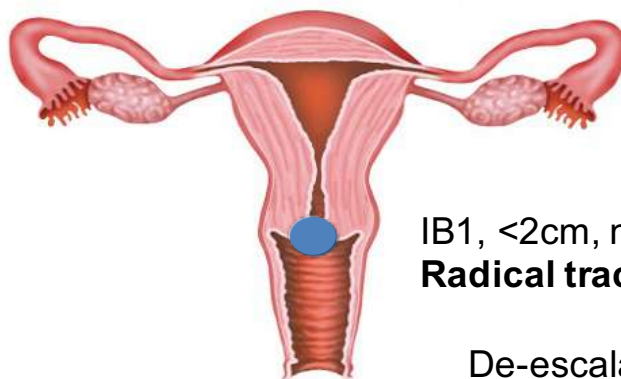


New french recommendations (INCA) in 2017:
Under colposcopy control to limit excision size
No systematic second procedure if no margin
HPV status more important in follow up

Fig. 1. The estimated association between the odds ratio (logarithmic scale) for preterm delivery and cone depth. *Adjusted for year of delivery, maternal age, smoking during pregnancy, and marital status. The association is fitted by a linear spline with knots placed at the quartiles (ie, 13, 16, and 20 mm). The reference level is the odds among deliveries not preceded by a loop electrosurgical excision procedure (circle). Noehr. Cone Depth of LEEP and Preterm Delivery. *Obstet Gynecol* 2009.

1997-2005 (552 678 singletons, 19049 preterm, 8 180 subsequent to Loop electrosurgical excision procedure): 6% increase in risk of preterm delivery per each additional millimeter of tissue excised (OR: 1,06 95% [1,03-1,09])
 LEEP: RR X2 / no LEEP
 2 or + LEEP: RR X4 / no LEEP

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IB1, <2cm, no LVSI, N-:
Radical trachelectomy

De-escalation ?
 (on going studies)

Radical trachelectomy

- Technique of Pr Dargent in 1987
- Conditions
 - Histological review
 - <2cm
 - No LVSI (discussed, demonstrated risk factor)
 - MRI: limited / isthms
 - Desire of pregnancy (fertility ?)
 - Examination: size of cervix after previous conization...
- During surgery
 - Pelvic lymphadenectomy
 - Frozen section for margin
 - Definitive cerclage

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Role of Imaging in Fertility-sparing Treatment of Gynecologic Malignancies¹ Rockall radiographics 2016

Table 2: MR Imaging Findings Used to Assess Eligibility for Trachelectomy

Length of the cervix from the external os to the internal os
Length of the endometrial cavity from the fundus to the internal os
Diameter of the tumor on three axes
Position of the tumor in the cervix
Tumor growth pattern (exophytic or diffusely infiltrating)
Distance of the proximal edge of the tumor to the internal os, parametrium, or vaginal fornix
Nodal enlargement (pelvic or para-aortic)
Incidental finding in other organs (ovaries, rectum, or bladder)

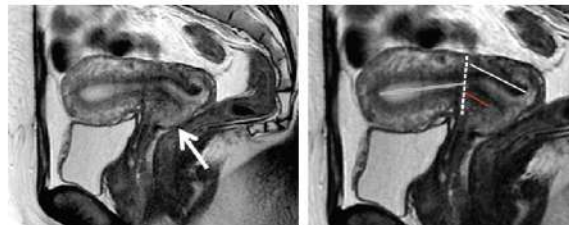
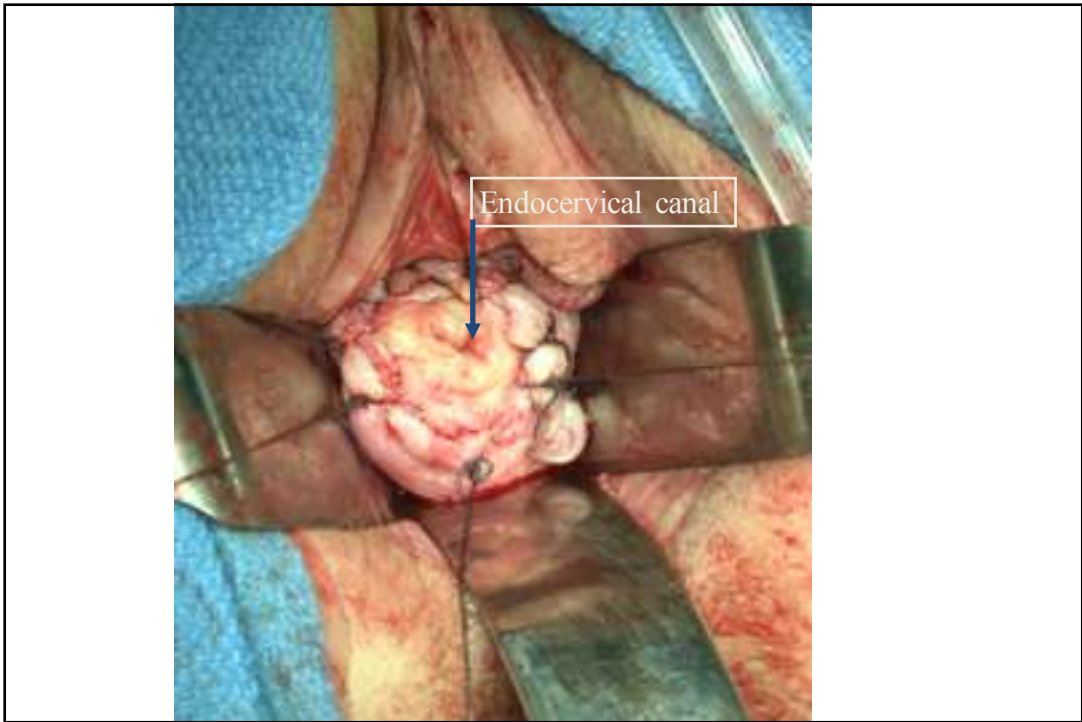
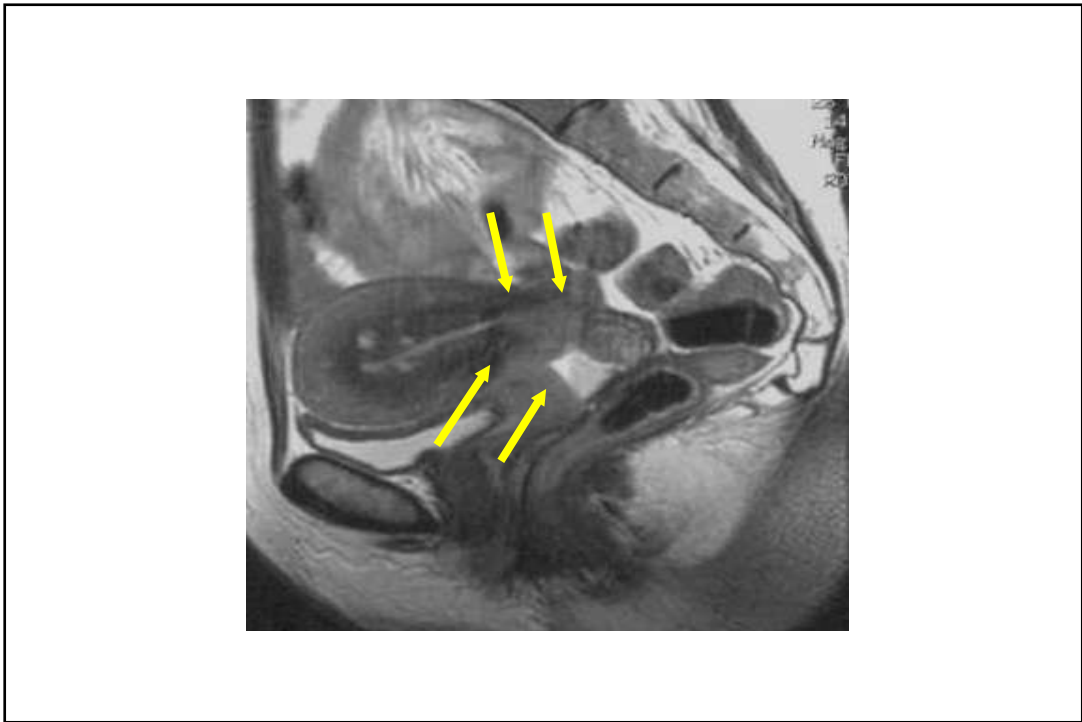


Figure 3. Assessment of eligibility for trachelectomy. (a) Sagittal T2-weighted MR image shows soft tissue with intermediate signal intensity (arrow), consistent with a cervical tumor, in the anterior lip of the cervix. The tumor is smaller than 2 cm in diameter and more than 1 cm from the internal os, with no evidence of extrauterine extension. (b) Sagittal T2-weighted MR image shows the measurements that must be defined. Then, the length of the cervix from the internal os to the external os (solid white line), the length of the endometrial cavity from the fundus to the internal os (gray line), and the distance from the leading edge of the tumor to the internal os (red line) should be measured.

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Less radical surgery ?

- Review of rate of parametrial involvement if N-, <2cm, no LVSI: 0.6% (Uzan 2009, Schmeler 2011)

Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care?^{1,2*}

Pedro T. Ramirez ^{1,2*}, Rene Pareja ³, Gabriel J. Rendón ³, Carlos Millan ⁴, Michael Frumovitz ², Kathleen M. Schmeler ²

Gynecol oncol 2014

- 3 on going trials
 - ConCerv (Schmeler): cohorte with less radical surgery, 25/100
 - SHAPE (Plante): randomization radical vs non radical, 700 pts
 - GOG 278 (Covens): quality of life after non radical surgery, 200 to 600 pts

Clinical recommendation radical trachelectomy for fertility preservation in patients with early-stage cervical cancer.
Int Gyn Cancer, Schneider et al 2012

- Review VRT-ART
- If < 2 cm, Recurrence rate 3-6%
- Death rate 2-5%
- Same fertility
- Risk of preterm delivery RR=2-3
- More info on VRT / ART
- >2cm, chemo and RT: option but limited experience

Fertility after trachelectomy (Bentivegna fertil steril 2016)

TABLE 1

Details of the main fertility results of this systematic review according to FSS procedures for cervical cancer.

Parameter	Simple trachelectomy/cone resection	Dargent procedure	Radical trachelectomy, laparotomy	Radical trachelectomy, minimally invasive	Neoadjuvant chemotherapy	Total
Patients	212	1,355	735	314	161	2,777
Patients excluded ^a	12	150	93	37	13	289
Recurrences	4				7	106
Infertile patients	4				19	229
No. of pregnancies	103				93	944
Fetal loss, 1st trimester	9				12	121
Fetal loss, 2nd trimester	5				5	54
Fetal loss, 1st or 2nd trimester undetermined	0				0	11
Interruption-abortion	2				0	24
Ectopic pregnancy	1				1	8
Drugging pregnancy	14				4	60
Preterm delivery (<6 WG)	8				11	223
Between 22 and 28 WG	1				2	28
Between 29 and 33 WG	3				5	53
Between 34 and 36 WG	0				2	64
Undetermined or other cutoff	4				2	78
Pregnancy rate ^b	22/39 (56)	241/424 (57)	135/916 (44)	57/67 (65)	60/78 (77)	515/938 (55)
Live birth rate ^c	51/69 (74)	308/460 (67)	120/175 (68)	50/64 (78)	71/93 (76)	600/861 (70)
Prematurity rate ^d	8/51 (15)	113/285 (39)	59/104 (57)	25/50 (50)	11/71 (15)	216/561 (38)

Note: Values are number (percentage).

^a Patients excluded for oncologic reasons depriving them of FSS management.

^b Pregnancy rate determined in series with complete data on the total number of patients attempting to become pregnant and the number of them succeeding.

^c Live birth rate determined in series with complete data about the total number of pregnancies and the number of live births. Ratio between the 2 was then determined.

^d Prematurity rate determined in series with complete data about the number of live birth deliveries and the number of premature deliveries. Ratio between the 2 was then determined.

Bentivegna. Conservative treatment of cervical cancer. *Fertil Steril* 2016.

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Sexuality after trachelectomy

Table 2
Localized cervical cancer; comparison of overall sexual satisfaction and sexual QOL.^a

	N	Sexual Satisfaction (%)	OR (95% CI) ^{b,c}	Sexual Health QOL ^d (mean WHO-BREF score)	p-value ^{b,c}
FSS	83	56%	0.8 (0.4–1.6)	15 +/- 2.9	0.08
No FSS	84	60%		16 +/- 4.1	

Abbreviations: QOL = quality of life, FSS = fertility-sparing surgery, CKC (cold-knife cone), OR = odds ratio.

^a All subjects in the group had at least one ovary and had no exposure to radiation.

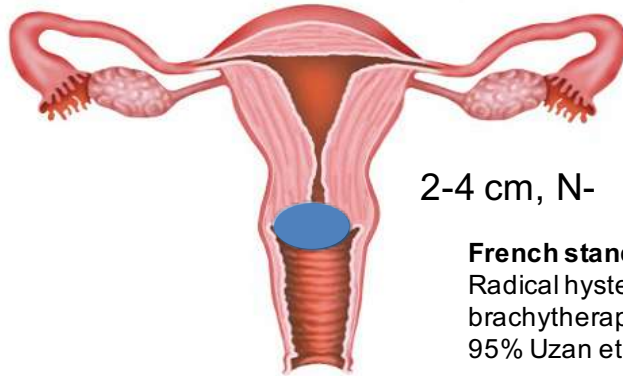
^b Odds ratio calculated from logistic regression, p-value from t-test comparing groups.

^c Unless otherwise noted, p-value remained non-significant after controlling for current age. Menstrual history consistent with menopause did not independently affect sexual satisfaction or sexual health QOL in the FSS group.

^d WHOQOL-BREF raw scores range from 4 to 20, with higher scores reflecting greater QOL.

- While FSS may allow for post-treatment fertility, it may not confer a significant benefit with regard to sexual satisfaction or sexual QOL.
- Decision to perform FSS should not be dictated based on preservation of sexual functioning.

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2-4 cm, N-

French standard:

Radical hysterectomy (RH) or
brachytherapy-RH (5 year survival rate
95% Uzan et al 2012)

Option to spare fertility:

Neoadjuvant chemotherapy (NAC)
trachelectomy / conization

Oncological and pregnancy outcomes after high-dose density
neoadjuvant chemotherapy and fertility-sparing surgery in
cervical cancer

Gynecol oncol 2014

Helena Robova^a, Michael J. Halaska^a, Marek Pluta^a, Petr Skapa^b, Jan Matecha^a, Jiri Lisy^c, Lukas Rob^{a,*}

- 28 patients <35y, > 2 cm or >50% stroma infiltration
- Dose-dense NAC (cisplatin-ifo for SCC/ cisplatin-doxo for ADK)
- Pelvic laparoscopy and simple trachelectomy
- Median FU 42 months
- 10 lost fertility
- 10/20 pregnant, 10 babies/ 8 wo (4 preterm)
- 20% recurred (2/4 DCD)

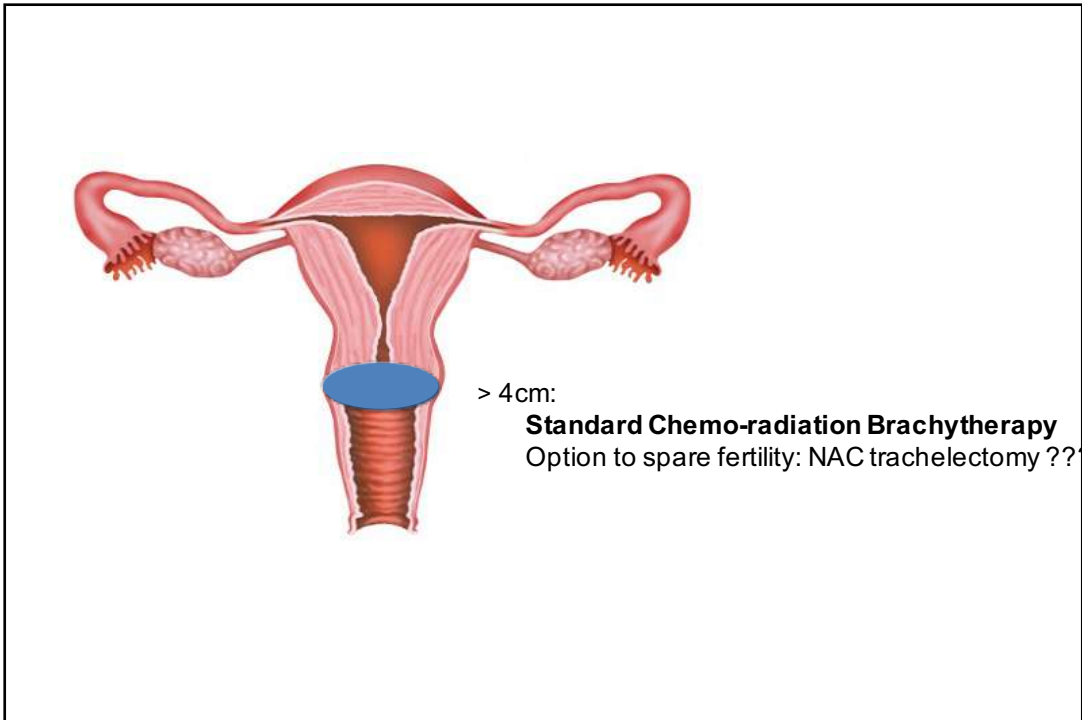
Conclusions. Downstaging by NAC in IB1 and IB2 cervical cancer before fertility-sparing surgery is still an experimental procedure, but shows some promise. Long-term results in relation to oncological outcome for this concept are still needed.

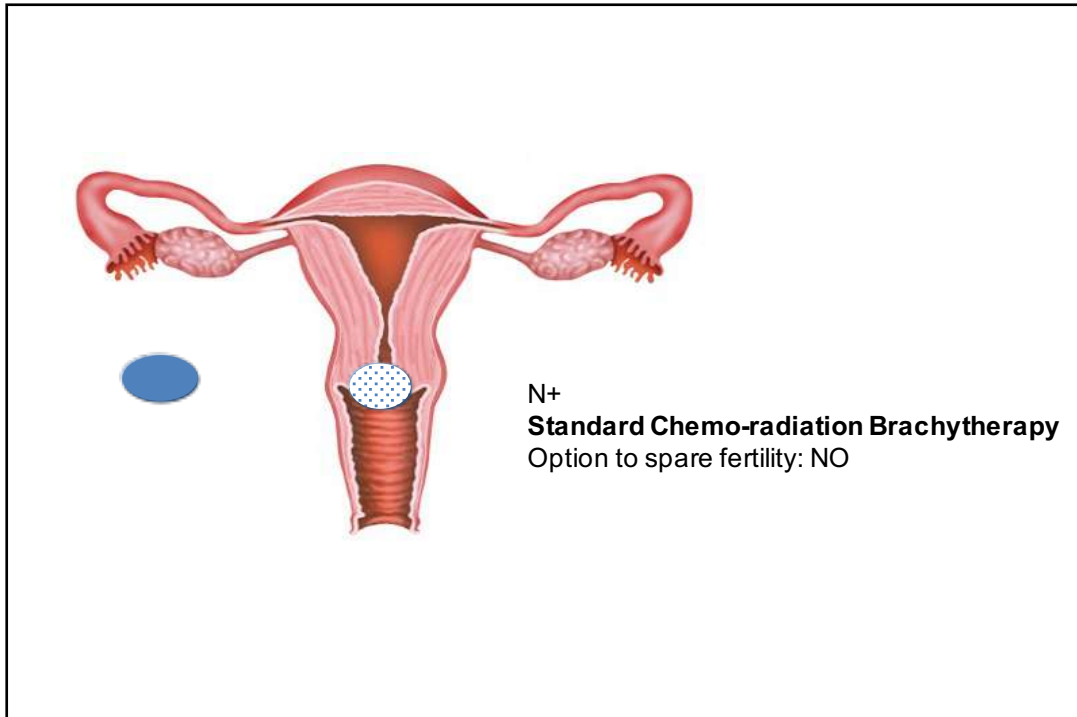
Author et al. (Year)	Scheduled for IS	Underwent IS	IS (cm)	Chemotherapy regimen	Number of courses	Surgery after NACT	Residual disease	Outcomes (recurrence follow-up)
Kobayashi et al. 2012 ¹⁰	1	1	IB1 (30 mm)	Cisplatin, ifosfamide, paclitaxel, carboplatin	4	CR	No residual disease	No recurrence (median 48 months)
Hains et al. 2016, 2018 ¹¹	4	4	IB1 (30 mm, 30 mm, 30 mm, 30 mm)	7 cisplatin, ifosfamide, docetaxel, cisplatin, gemtuzumab	7	Pelvic LND+VBT	3 no invasive residual disease	No recurrence
Liveri et al. 2008 ¹²	1	1	IB1 (20 mm)	Cisplatin, ifosfamide	1	Pelvic LND+VBT	Final residual disease 5 mm	Not reported
Marchetti et al. 2017 ¹³	7	7	2 IB1 (31 mm, 30x30 mm), 2 IB2, 3 IB2 (4-6 mm)	Cisplatin, paclitaxel, ifosfamide, cisplatin, paclitaxel, epirubicin	2 or 4	Pelvic LND+VBT	3 no invasive residual disease, 1 residual disease, 2 partial response	No recurrence (median 27 months)
Singh et al. 2017 ¹⁴	1	1	IB1 (15 mm)	Carboplatin, paclitaxel	7	Pelvic LND+VBT	Residual disease 20 mm	No recurrence (median 14 months)
Falka et al. 2017 ¹⁵	1	1	IB1 (15 mm)	Cisplatin, paclitaxel, docetaxel	7	Pelvic LND+VBT	No invasive residual disease	No recurrence (median 18 months)
Talasila et al. 2017 ¹⁶	1	1	IB2 (20 mm)	Cisplatin, paclitaxel, ifosfamide	7	Pelvic LND+VBT	No residual disease	No recurrence (median 24 months)

112 patients
Cisplatin-ifosfamide FU / cisplatin ifosfamide paclitaxel
6 recurrences (4 / 28 in the largest series)

Author et al. (Year)	n	n	IS (cm)	Chemotherapy regimen	Number of courses	Surgery after NACT	Residual disease	Outcomes (recurrence follow-up)
Rebecq et al. 2015, 2016 ¹⁷	28	20	21 IB1 (21 base, 8-30 mm), 7 IB2	7 cisplatin, ifosfamide, 7 cisplatin, ifosfamide, docetaxel	7	Pelvic LND+VBT	12 mm, 0 no residual disease, 11 residual disease < 3 mm, 11 residual disease > 3 mm	3 local and 1 distant recurrence, 2 died from disease (median 47 months)
Griffiths et al. 2013, Vanilinas et al. 2012, Larocca et al. 2014 ¹⁸	20	20	14 IB1 (6-70 mm), 5 IB2, 1 IB3	1 cisplatin, paclitaxel, 7 cisplatin, paclitaxel, ifosfamide	2 or 3	VBT (in 18 pts), 3 none yet done	3 no invasive residual disease, 4 residual disease < 5 mm, 4 residual disease > 5 mm	3 distant recurrence, 20 months (median 27 months)
Liaw et al. 2014 ¹⁹	7	7	IB1 (30 mm)	7 cisplatin, ifosfamide, paclitaxel, carboplatin	7	Pelvic LND+VBT	Residual disease 10 mm	No recurrence (median 66 months)
Van Gert et al. 2014 ²⁰	3	3	3 IB1	Cisplatin, paclitaxel	6 (weekly)	Pelvic LND+VBT (invasive disease)	Residual disease 1 mm, 4 mm, and 5 mm	No recurrence (5, 21, and 65 months)
Sahli et al. 2015 ²¹	11	9	10 IB1 (4-12 cm), 1 IB2	7 cisplatin, paclitaxel, ifosfamide, 3 cisplatin, paclitaxel	7 (weekly), 2 (bi-weekly)	7 CR, 3 local recurrence	0 no residual disease, 2 residual disease (one with possible margin), 1 progressive disease not treated with recurrence	3 local recurrence (median 58 months)
Skaif et al. 2015 ²²	1	1	IB1 (15 mm)	Cisplatin, ifosfamide, paclitaxel	7	Laparoscopic radical trachelectomy	Residual disease 10 mm	No recurrence (median 5 months)
Hawthorn et al. 2017 ²³	1	1	IB1 (45 mm)	Cisplatin, ifosfamide, fluorouracil	Unknown	Pelvic LND+VBT	Unknown	No recurrence (median 66 months)

Review
 Bentivegna et al
 Lancet oncol 2016





To inform patients

- Risk of non eligibility during surgery (N+ or invaded margin in frozen section)
- Switch to Chemo-radiation if N+
- Results on fertility and pregnancy after this procedure
- De-escalation of surgery for limited lesions ?
- Increase indications of conservative treatment ???

How to improve our management ?

- To evaluate
 - stage,
 - desire and needs of the patient
- To anticipate
 - Risk of modification of treatment planification
 - Explain all the possibilities
 - Evolution of treatments (up-to-date)
- To collaborate
 - Imaging
 - Early consultation in oncofertility (network)
 - Learn from one other-international register (patient included)

Livebirth after uterus transplantation

Mats Brännström, Liza Johannesson, Hans Bokström, Niclas Kuvarström, Johan Måline, Perilla Dahm-Köhler, Anders Enskog, Milan Milenkovic, Jona Ekberg, Cesar Diaz-Garcia, Markus Gabel, Ash Hancjfy, Henrik Hagberg, Michael Olsson, Lars Nilsson

Lancet 2014

- Brannstrom team

Easier to preserve than to restore
(for now...)

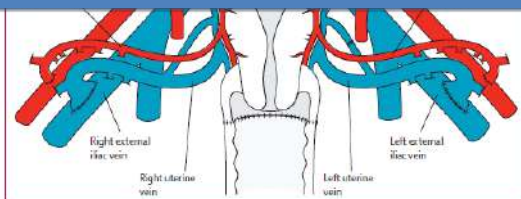


Figure 1: Schematic drawing of the vessel connections of the transplanted uterus

9 patients (8 Rokitanski, 1 cervical cancer)
2 graft removal
7 persistent (1 year report in fertile steril 2015 Jan)

5 livebirth to the last report (2016)