

Follow-up

- ❖ Post trachelectomy / cone
 - ❖ Need for **PROLONGED FOLLOW-UP**
 - ❖ Experienced gyn-onc / colposcopists
 - ❖ **HPV testing and vaccination**

Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: a systematic review and meta-analysis

Qing Zhang^{1,2,*}, Wenhui Li^{1,5,*}, Margaux J. Kanis³, Gonghua Qi¹, Minghao Li⁴, Xingsheng Yang¹ and Beihua Kong^{1,2}

60 studies: 17 **cone** and 43 **RT**

N=**2854** patients; 375 cone and 2479 RT

Stage IB1: 44% cone vs 80% RT

Recurrence rate:

- Stage IA: 0.4% vs 0.7%
- Stage IB1: 0.6% vs 2.3%

CONCLUSION: Fertility-sparing treatment including CON or RT for eCC is feasible and carefully selected women can preserve fertility and achieve pregnancy resulting in live births. **CON seems to result in better pregnancy outcomes than RT with similar rates of recurrence and mortality.**

Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature

Enrica Bentivegna, M.D.,^a Amandine Maulard, M.D.,^a Patricia Pautier, M.D.,^b Cyrus Chargari, M.D., Ph.D.,^c Sebastien Gouy, M.D., Ph.D.,^a and Philippe Morice, M.D., Ph.D.,^{a,d,e}

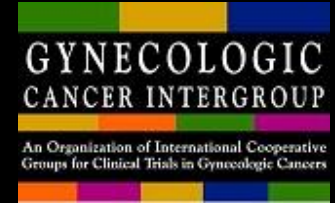
- Review of 2777 patients; **944 pregnancies**
- Overall fertility rate: **55%**
- Pregnancy rate: better after **vaginal**/MIS RT compared to abdominal RT
- Live birth rate: similar (**70%**)
- Prematurity (**38%**): significantly lower after **ST/Cone**
- 2nd-T loss: related to PROM

Prospective trials

↻Concerv

↻GOG-278

ConCerv (G-GOC)



Cervical Cancer-Conservative Management

Cone/Simple Hysterectomy + SLN Only

Stage IA2-IB1 (<2 cm) LVSI (-); SCC G1-3; ADK G1-2

Study Design: Prospective Phase II

Sponsor(s): None

Planned No. of patients: 100

Current accrual: 81

Other important information:

14 Sites Overall

Primary: MD Anderson

ConCerv Preliminary Data (N=160)

➤ **Evaluable patients (n=81)**

- 34 simple hysterectomy + nodes (42%)
- 31 cone and nodes (38.2%)
- 16 nodes only (19.8%) – simple hysterectomy inadvertently performed with unexpected diagnosis of invasive cancer meeting inclusion criteria with negative margins (“cut through hysterectomy”)

➤ **Not evaluable (n=79):**

- **76 ineligible** after MD Anderson **pathology review**
- 1 cancelled due to (+) pregnancy test
- 1 declined surgery
- 1 patient did not have surgery on protocol due to study hold (amendment was submitted)

ConCerv Preliminary Data

∞ 5 patients with positive nodes (6.2%)

- IA2 G2 SCCA (No visible tumor) x 2
- IB1 G2 SCCA (No visible tumor)
- IB1 G2 SCCA (Visible tumor 1.8 cm)
- IB1 G3 SCCA (Visible tumor less than 2cm)

∞ One patient with residual disease at hysterectomy

- Multiple previous cones for AIS
- No changes to inclusion criteria

∞ 3 recurrences (3.7%)

- Deep stromal invasion and CIN3 at margins (Inclusion criteria changed after first recurrence)
- Recurrent **pelvic mass** 9 months after simple hysterectomy
- Metastatic **inguinal lymph node** 9 months after simple hyst

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PROTOCOL GOG-0278
EVALUATION OF PHYSICAL FUNCTION AND QUALITY OF LIFE (QOL) BEFORE
AND AFTER NON-RADICAL SURGICAL THERAPY (EXTRA FASCIAL
HYSTERECTOMY OR CONE BIOPSY WITH PELVIC LYMPHADENECTOMY) FOR
STAGE IA1 (LVSI+) and IA2-IB1 (≤ 2 CM) CERVICAL CANCER
NCI Version Date 07/10/2012

POINTS:
PER CAPITA - 20
MEMBERSHIP - 6

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SCHEMA

Women with **IA1– IB1 ($\leq 2\text{cm}$)** carcinoma of the cervix
who have been consented for surgery
will be approached for study participation and entered on study.

Conization with pelvic
lymphadenectomy
(fertility preservation)
Group

N=220

Simple hysterectomy
with pelvic
lymphadenectomy
(no wish for future fertility)
Group

Medical Information/Physician Checklist:

Medical extraction form CTCAE v. 4.0 criteria

Preoperative Study Survey (15 min to complete):

Bladder and Bowel Function Items

Female Functioning Index & 2 PROMIS items

GCLQ – Gyn Cancer Lymphedema Questionnaire

Functional Assessment Cancer Therapy FACT-Cx

Impact of Events Scale (IES)

Conization Group only Reproductive Items (ICF & RCS)

Medical Information/Physician Checklist:

Medical extraction form CTCAE v. 4.0 criteria

Preoperative Study Survey (15 min to complete):

Bladder and Bowel Function Items

Female Functioning Index & 2 PROMIS items

GCLQ – Gyn Cancer Lymphedema Questionnaire

Functional Assessment Cancer Therapy FACT-Cx

Impact of Events Scale (IES)

Simple Trachelectomy-Cone

➤ Valuable less radical option for women with **LOW-RISK small volume** disease

▣ < 2 cm

➤ Patient selection critical

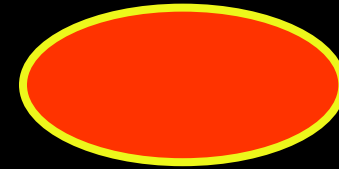
➤ Long-term follow-up essential

Conclusion

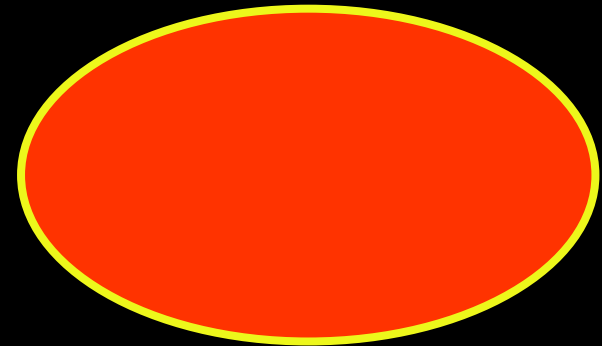
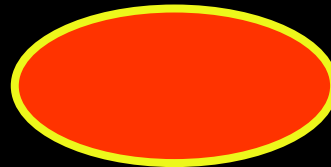
➤ Change FIGO classification?

▣ Sub-divide stage **IB1**

• a: < 2 cm



• b: ≥ 2 cm
 < 4 cm





CLINICAL STAGE^b

PRIMARY TREATMENT (FERTILITY SPARING)^e

Stage IA1
(no lymphovascular
space invasion
[LVSI])

Cone biopsy^f with negative margins^g
(preferably a non-fragmented specimen with 3-mm negative margins)^g
(If positive margins, repeat cone biopsy or perform trachelectomy)

[See Surveillance \(CERV-10\)](#)

Stage IA1
(with LVSI)
and
Stage IA2

Cone biopsy^f with negative margins^g
(preferably a non-fragmented specimen with 3-mm negative margins)^g
(if positive margins, repeat cone biopsy or perform trachelectomy)
+ pelvic lymph node dissection
± para-aortic lymph node sampling (category 2B)
(Consider sentinel lymph node [SLN] mapping)^h
or
Radical trachelectomy + pelvic lymph node dissection^h
(± para-aortic lymph node sampling [category 2B])
(Consider SLN mapping)^h

[See Surveillance \(CERV-10\)](#)

Stage IB1^d

Radical trachelectomy
+ pelvic lymph node dissection^h
± para-aortic lymph node sampling
(Consider SLN mapping)^{h,i}

[See Surveillance \(CERV-10\)](#)

^b[See Principles of Imaging \(CERV-A\).](#)

^dFertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and adenoma malignum are not considered suitable tumors for this procedure.

^eNo data to support a fertility-sparing approach in small neuroendocrine tumors, gastric type adenocarcinoma, or adenoma malignum (also known as minimal deviation adenocarcinoma). Total hysterectomy after completion of childbearing is at the patient's and surgeon's discretion, but is strongly advised in women with continued abnormal pap smears or chronic persistent HPV infection.

^fCold knife conization (CKC) is the preferred method of diagnostic excision, but loop electrosurgical excision procedure (LEEP) is acceptable, provided adequate margins and proper orientation are obtained. Endocervical curettage (ECC) may be added as clinically indicated.

^gNegative for invasive disease or histologic high-grade squamous intraepithelial lesion (HSIL) at margins.

^h[See Principles of Evaluation and Surgical Staging \(CERV-B\).](#)

ⁱFor SLN mapping, the best detection rates and mapping results are in tumors <2 cm.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NACT and Fertility Sparing

- ⌘ How to best manage young women with **larger** size lesions/bulky IB1-IB2 (**2-4 cm**)
 - ▣ Preservation of **fertility** and **ovarian** function
 - ▣ **Oncologic** outcome
 - ▣ **Obstetrical** outcome

NACT and Fertility Sparing

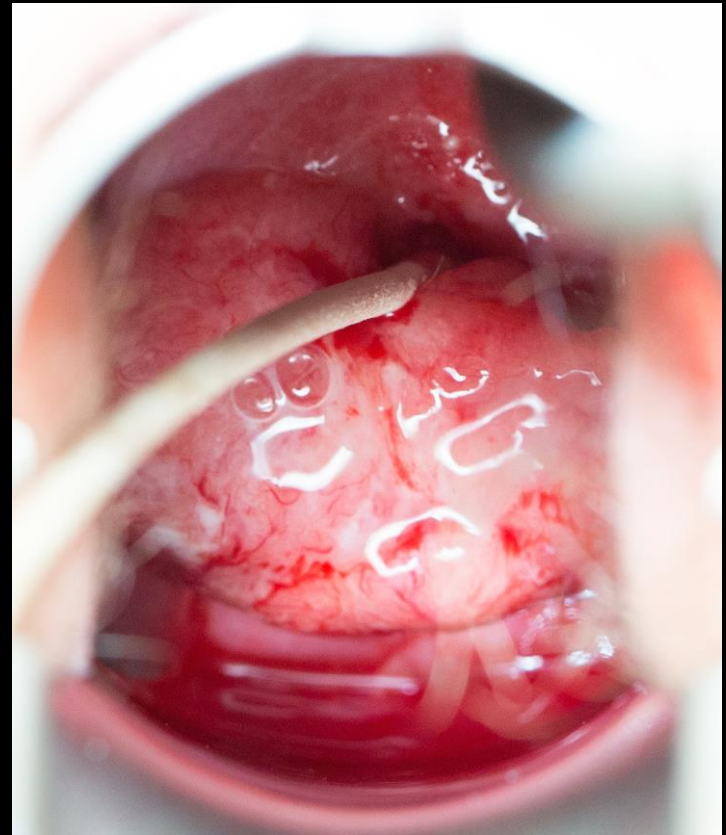
↻ 27 y.o woman G0P0

↻ Stage IB1

↻ 3.5 cm adenoca

Upfront Trach ?

NACT + FPS ?



NACT and Fertility Sparing

∞ Management options for patients with larger size lesions

- **Upfront Radical Trachelectomy**
- **NACT followed by fertility-preserving surgery (FPS)**

Upfront ART: lesions > 2 cm

	N	Fertility spared	Node Positivity	Recurrences	Pregnancies
Wethington , 2013	29	9 (31%)	13 (45%) *	1/29 (11%)	1/3
Lintner, 2013	45	31 (69%)	13 (29%)	4/31 (13%) **	4/8
Liu, 2013	62	55 (89%)	6 (9.8%)	0	3/9
	136	95 (70%)	32 (24%)	5/122 (5.3%)	8/20 (40%) 8/95 (8.9%) 8/136 (5.8%)

MSKCC: SLN mapping and ultrastaging

Hungarian series: 14 ptes who had rad hyst excluded from analysis

Plante M. Internat J Gynecol Cancer 2015 May;25(4):722-8.

Abdominal Trachelectomy

- **Wider parametria** and more radical surgery can be obtained with ART
- ART can be performed in **larger size lesions**
- High rate of **adjuvant treatment** post trachelectomy
 - Impact on fertility
 - Impact on ovarian function
 - Impact on QoL



Fig. 3. Unfixed specimen of abdominal radical trachelectomy demonstrating vaginal margin and at least 4 cm of parametrial tissue continuous with the cervix.

Indications for adjuvant RT

LVSI	Stromal Invasion	Tumor Size
Positive	Deep 1/3	Any
Positive	Middle 1/3	> 2
Negative	Superficial 1/3	> 5
Negative	Deep or Middle 1/3	> 4

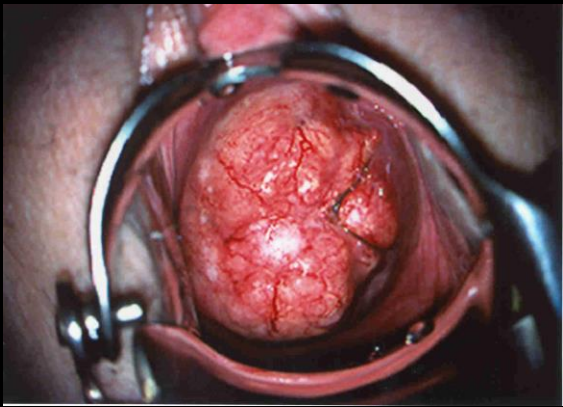
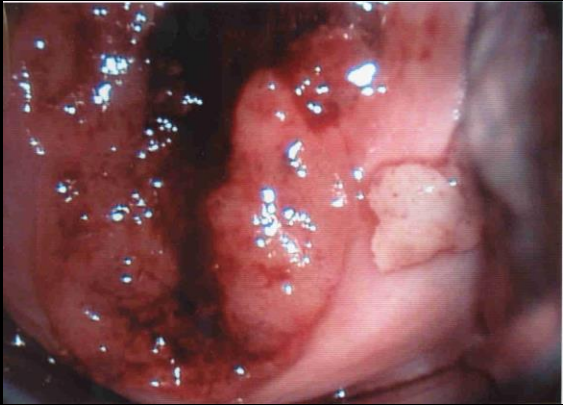
Sedlis criteria : needing **2 or more** of these factors

- LVSI involvement
- Deep stromal invasion (middle or deep third)
- Size > 4 cm

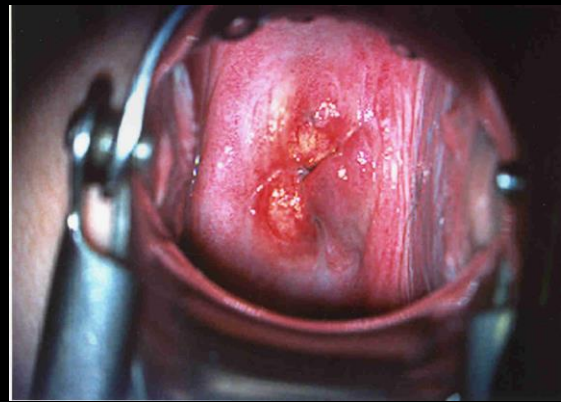
NACT + FPS

➤ NACT option followed by fertility-preserving surgery (FPS)

Neoadjuvant chemotherapy



Pre-chemo



Post-chemo

NACT + fertility preserving surgery

	N	Chemotherapy Regimen	Procedure	Optimal Response to NACT (CR + OPR)	Node Positivity
Maneo	21	TIP x 3	LPLND + cone	17/21 (81%)	2
Plante	3	TIP x 3	LPLND + RVT	3/3 (100%)	0
Marchiole	7	TIP/TEP x 3	LPLND + RVT	4/7 (57%)	0
Lanowska	18	TIP/TP x 2-3	LPLND + RVT	14/18 (78%)	2
Robova	28	CI q 10d x 3 CA q 10d x 3	LPLND + SVT	17/28 (61%)	2
Total	77			55/77 (71%)	6/77 (7.8%)

Plante M. Internat J Gynecol Cancer 2015 May;25(4):722-8.

	Recurrences	Death	Fertility Preserved	Pregnancy/ Attempted	Pregnancy Outcome
Maneo	0	0	16/21 (76%)	10/9	1 FTM 5 preterm 2 SVD (term) 2 CS (term)
Plante	0	0	3/3 (100%)	4/3	1 FTM 1 preterm , 2 term
Marchiole	0	0	6/7 (86%)	1/1	1 ongoing
Lanowska	1/18 (5.5%)	0	17/18 (94%)	7/5	1 FTM 1 ectopic 1 ongoing 2 preterm, 2 term
Robova	4/20 (20%)	2/20 (10%)	20/28 (71%)	13/10	1 FTM 2 STM 2 ongoing 3 preterm, 5 term
Total	5/69 (7.2%)	2/69 (2.9%)	62/77 (80%)	35/28	11 FT loss (31%) 11 preterm (31%) 13 term (37%)

Long-Term Clinical Benefits of Neoadjuvant Chemotherapy in Women With Locally Advanced Cervical Cancer

Validity of Pathological Response as Surrogate Endpoint of Survival

Alessandro Buda, MD,*† Andrea Alberto Lissoni, MD,*† Irene Floriani, PhD,†‡ Elena Biagioli, MSc,†‡ Chiara Gerardi, MSc,†‡ Cristina Bonazzi, MD,*† Stefania Chiari, MD,*† Luca Locatelli, MD,§ Tiziana Dell'Anna, MD,*† Mauro Signorelli, MD,*† Costantino Mangioni,*† and Rodolfo Milani*†

Response to NACT is a good surrogate endpoint of survival in patients with LACC.

NACT + fertility preserving surgery

➤ Substantial response to NACT

- CR/OPR: **71%**

➤ Recurrence rate / death

- **Higher in Sub Optimal PR**

➤ Node positivity is much lower post NACT

➤ Fertility preservation high: 80%

➤ Fertility/obstetrical outcome good

Unresolved issues

- ⌘ Staging LN dissection prior to NACT ?
- ⌘ Simple vs radical trachelectomy vs cone post NACT ?
- ⌘ What is best chemotherapy regimen ?

NACT + fertility preserving surgery

➤ Should a **staging lymph node evaluation** be done prior to NACT ?

- ▣ Probably **yes**

NACT + fertility preserving surgery

⌘ Advantage of LN staging

- ▣ Rule out patients with metastatic disease
- ▣ Offer non-surgical treatment (CT/RT)

⌘ Disadvantage of LN staging

- ▣ Exclude some patients with minimal lymph node involvement who might have cleared the LN mets with the NACT

NACT + fertility preserving surgery

IB2-IIA2 (n=304 ptes)

Procedure	Node positivity
Primary surgery (154)	25.6%
NACT + surgery (150)	8.1%

Response rate to NACT was 72%

NACT + fertility preserving surgery

➤ Should a **radical** or a **simple** trachelectomy or a **cone** be done post NACT ?

NACT + fertility preserving surgery

➤ Radical / simple trachelectomy / cone post NACT ?

➤ In good chemotherapy responders

- Node negative patients
- Minimal / no residual disease post NACT
- The chances of finding occult **parametrial infiltration** are probably very low
- Cone / Simple Trachelectomy sufficient ??

NACT + fertility preserving surgery

➤ Optimal chemotherapy regimen

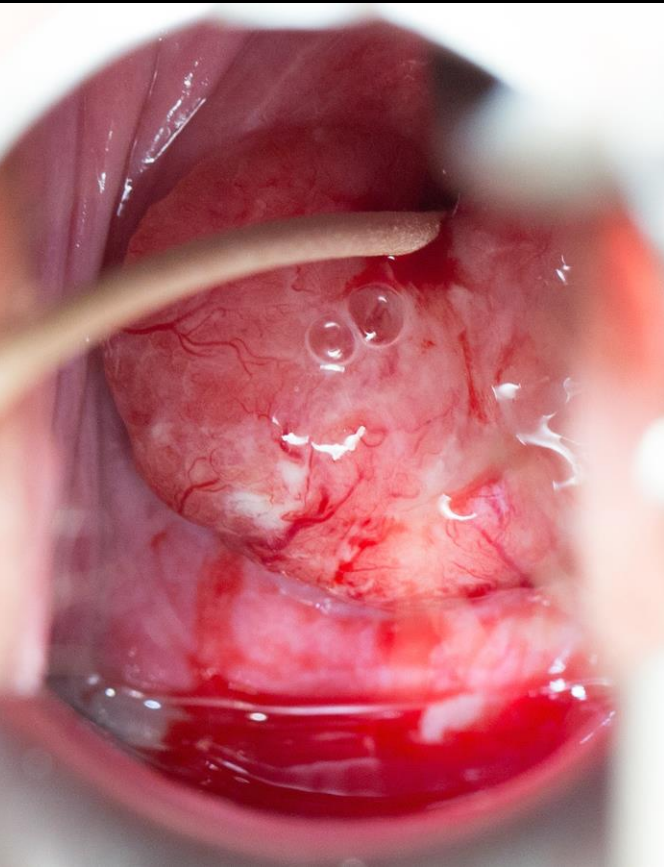
Chemotherapy regimen

Italian Q 3 weeks x 3	Taxol 175 mg/m ²	Ifosfamide 5g/m ²	Cisplatin 75 mg/m ²
“Ovarian” Q 3 weeks x 3	Taxol 175 mg/m ²		Carbo AUC 6
Dose dense Weekly x 9	Taxol 80 mg/m ²		Carbo AUC 2
“Belgian” Dose dense Weekly x 9	Taxol 60 mg/m ²		Carbo AUC 2.7
Prague regimen Q 10d x 3		Ifosfamide 2g/m ² Squamous	Cisplatin 75 mg/m ²
Prague regimen Q 10d x 3		Adriamycin 35mg/m ² Adenoca	Cisplatin 75 mg/m ²

9 weeks = 63 days

EORTC 55994 regimen

Dose dense Taxol-Carbo



Pre-chemoTx



After 3rd cycle

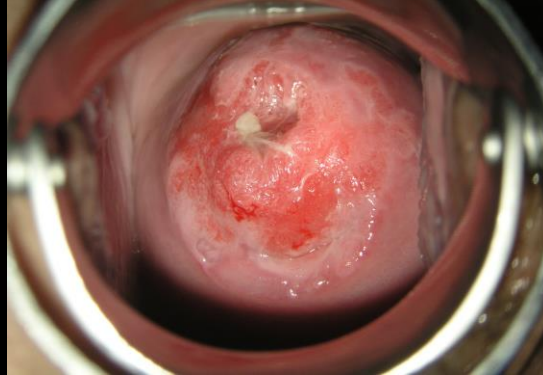


Neoadjuvant chemotherapy

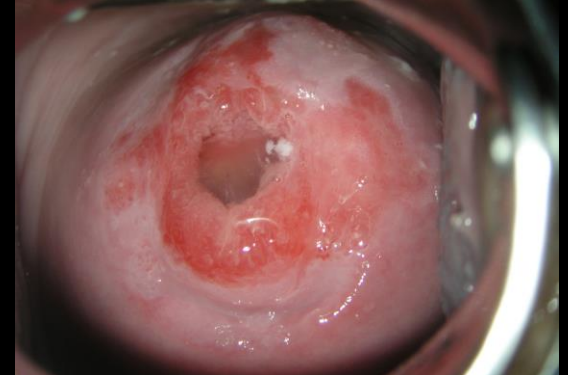
Dose-Dense Prague Protocol: q 10d x 3



Pre chemotherapy



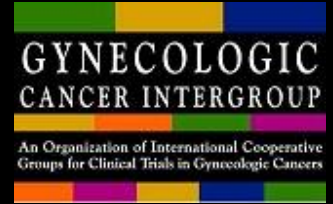
After one cycle of chemo



After 3 cycles of chemo

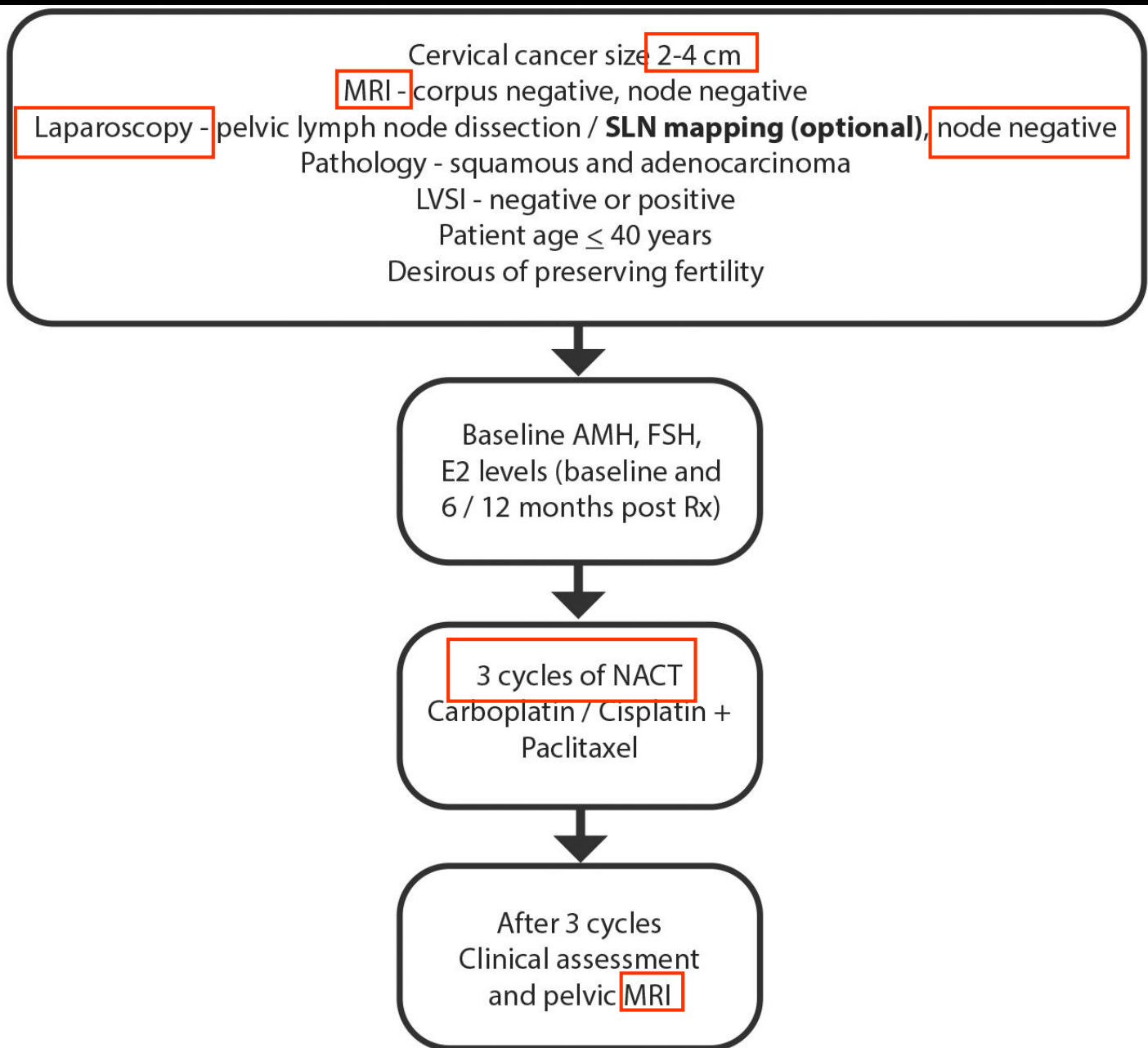
Courtesy of Lukas Rob, Prague

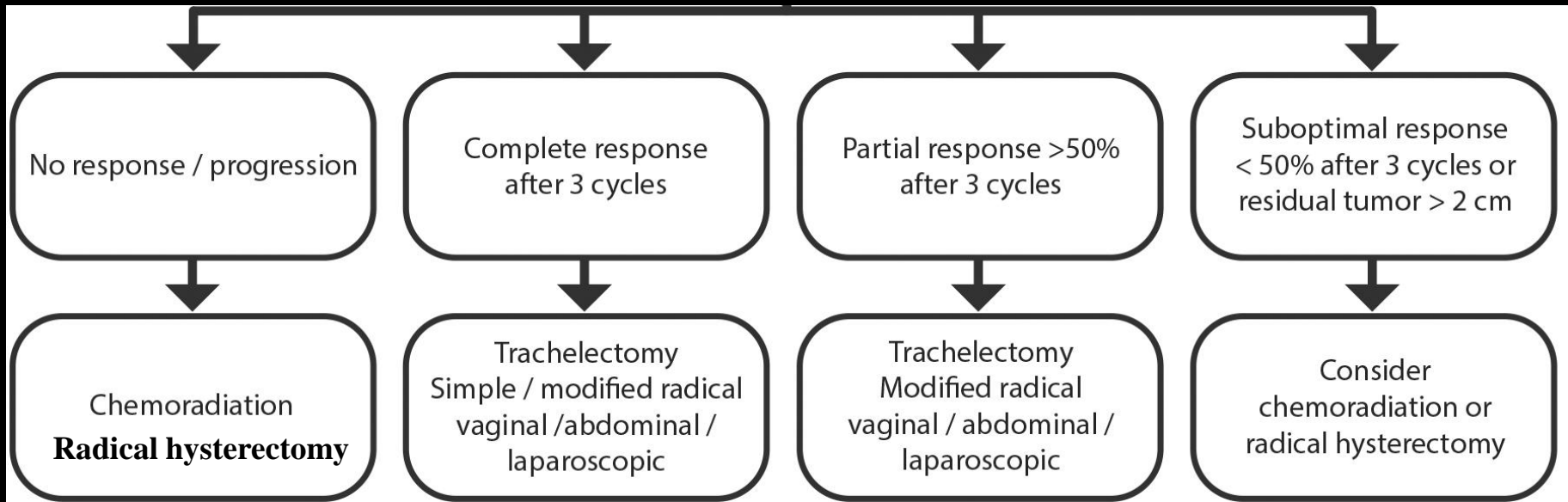
PROPOSAL



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

Marie Plante (CCTG)

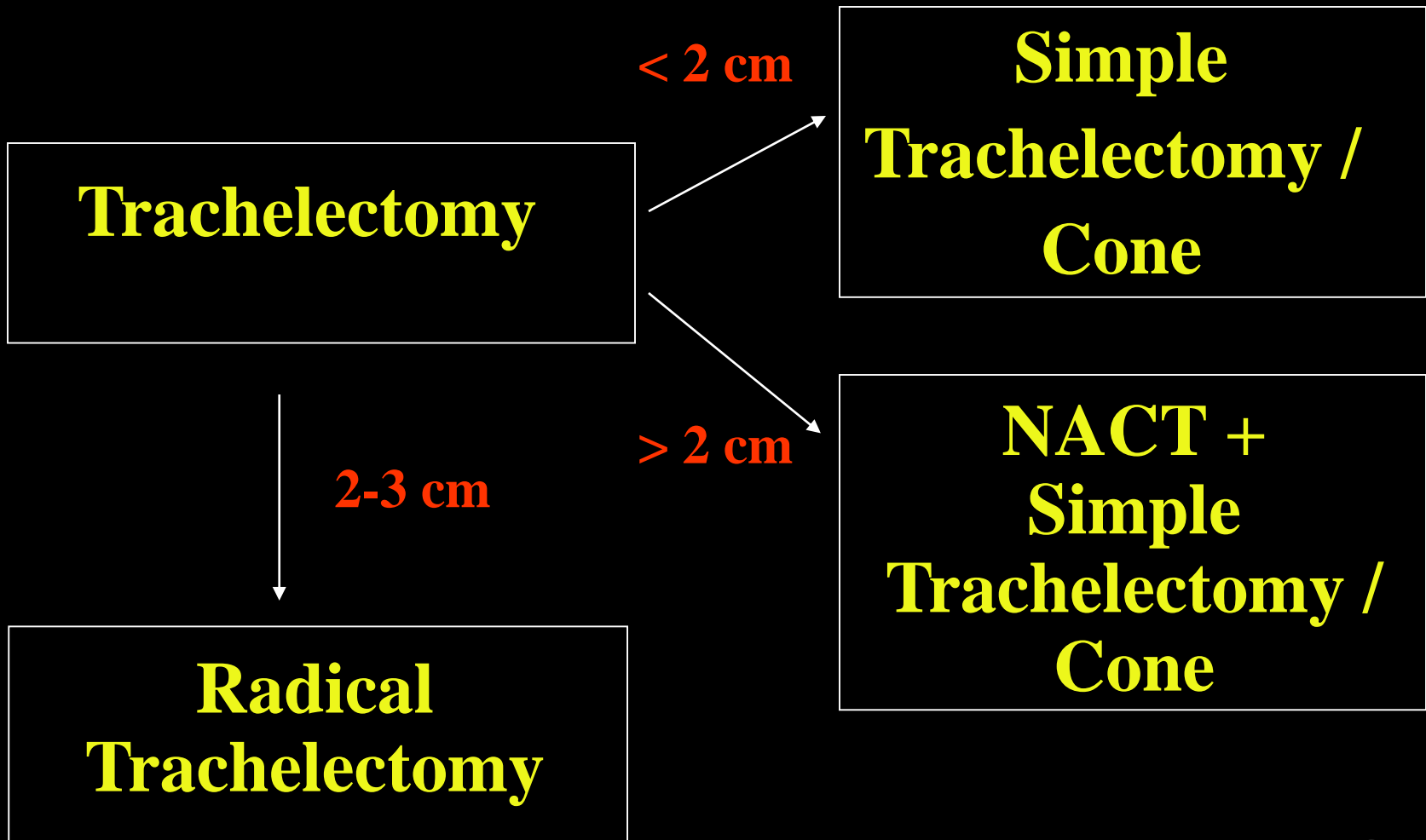




Adjuvant chemoradiation
(or radical hysterectomy)
Positive margins
Stromal involvement in outer 1 / 2
 ≥ 5 mm stromal invasion
< 10 mm margin

SUMMARY

Trachelectomy: The Future ?



Evolution in the management of cervical cancer

