Neo-adjuvant chemotherapy and fertility sparing surgery for stage IB1 cervix cancer (2-4 cm)

Marie Plante (NCIC)

Jeffrey Goh & Vivek Arora (ANZGOG)

GCIG Meeting Chicago – May 2015

CLINICAL STAGE	PRIMARY TREATMENT (FERTILITY SPARING)[d]	
Stage IA1 (no lymphovascular space invasion [LVSI])	Cone biopsy[e] with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (If positive margins, repeat cone biopsy or perform trachelectomy)	See Surveillance (CERV-10)
Stage IA1 (with LVSI) and Stage IA2	Cone biopsy[e] with negative margins (preferably a non-fragmented specimen with 3-mm negative margins- 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 [category 2B])[f] or Radical trachelectomy + pelvic lymph node dissection[f] (± para-aortic lymph node sampling [category 2B]) (Consider SLN mapping [category 2B])[f]	See Surveillance (CERV-10)
Stage IB1[c]	Radical trachelectomy + pelvic lymph node dissection[f] ± para-aortic lymph node sampling (Consider SLN mapping [category 2B])[f,g]	See Surveillance (CERV-10)

[c]Fertility-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.

[d]No data support a fertility-sparing approach in small cell neuroendocrine tumors or minimal deviation adenocarcinoma (also known as adenoma malignum). 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.

[e]Cold 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.

[f]See Principles of Evaluation and Surgical Staging (CERV-A).

[g]For SLN mapping (category 2B), 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NACT and Fertility Sparing

- How to best manage 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

- **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 ultra staging
Hungarian series: 14 ptes who had rad hyst excluded from analysis

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

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**

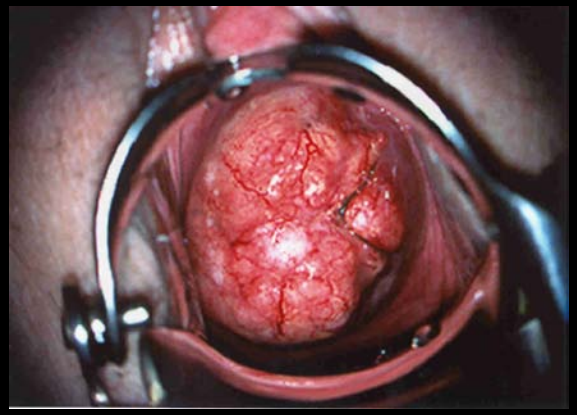
Abdominal Trachelectomy

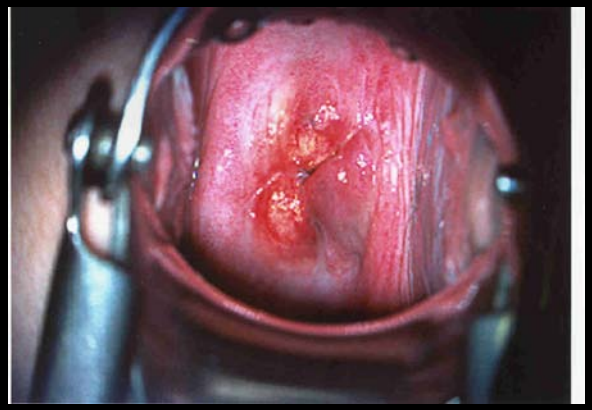
- Upfront ART technically feasible in bulky stage I cervical cancer
- Oncologic outcome good
- Obstetrical outcome limited
- High rate of adjuvant Tx post trachelectomy
  - Impact on fertility and ovarian function
  - Impact on QoL

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%)

All in suboptimal responders

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

NACT + fertility preserving surgery

- Substantial response to NACT
  - CR/OPR: 71%
- Recurrence rate
  - Worrisome in suboptimal responders
- Fertility preservation high: 80%
- Obstetrical outcome: good

Unresolved issues

- Staging lymph node dissection prior to NACT ?
- Radical vs simple trachelectomy vs cone post NACT ?
- Best chemotherapy regimen ?

NACT + fertility preserving surgery

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

NACT + fertility preserving surgery

Advantage of LN staging

- Allows triaging of pts with metastatic disease
- Option of non-surgical treatment (CT/RT)

Disadvantage of LN staging

- Exclude some patients with minimal LN involvement who might have cleared the LN metastasis with NACT

NACT + fertility preserving surgery

- Should a radical or a simple trachelectomy (cone) be done post NACT ?

NACT + fertility preserving surgery

- Simple / radical trachelectomy / cone
  - Very little data available
  - Trend towards less radical surgery in small volume cervical cancer (< 2 cm)

NACT + fertility preserving surgery

- In good chemotherapy responders
  - Node negative patients
  - Minimal / no residual disease post NACT
    - Gyn exam & MRI
  - The chances of finding occult parametrial infiltration are probably very low
  - Simple trach / cone sufficient?

NACT + fertility preserving surgery

- Optimal chemotherapy regimen

Optimal chemotherapy regimen

- **Taxol / Ifosfamide / Platinum (TIP)**
  - **Most widely used regimen**
  - **Toxicity of triple chemo regimen**
  - **Ifosfamide (alkylating agent)**
    - **gonadotoxicity**

Optimal chemotherapy regimen

- Systematic review
  - 17 studies / 1181 patients
  - Recurrent or metastatic cervical cancer
  - Comparing cisplatin and carbo + taxol
  - Conclusion: carboplatin represents a valid and less toxic alternative compared to cisplatin

Lorusso D . Gynecol Oncol 2014;133(1):117-23.

Optimal chemotherapy regimen

- A randomized, phase III trial of paclitaxel plus carboplatin (TC) versus paclitaxel plus cisplatin (TP) in stage IVb, persistent or recurrent cervical cancer: Japan Clinical Oncology Group study (JCOG0505) (n=253)
- Taxol 175 & Carbo AUC 5 q 3 wks
  - Non-inferior in terms of OS
  - More feasible
  - Less toxic

Kitagawa R et al. J Clin Oncol. 2015 Mar

Optimal chemotherapy regimen

- Dose-dense NACT chemo regimen
  - **Weekly Taxol/Carbo**
    - Taxol 60-80 mg/m2 and Carbo AUC 2
  - **Locally advanced** cervical cancer
  - Objective response rate (complete & partial)
    - Ranges from **68-87 %**

McCormack M. Br J Cancer 2013;108(12):2464-9.
Singh RB. Gynecol Oncol 2013;129(1):124-8.

Optimal chemotherapy regimen

- Another dose-dense chemo regimen
  - Taxol 80mg/m2 weekly (d 1,8,15)
  - Carbo AUC 6 q 3 weeks (d 1)
  - JGOG 3016 trial in ovarian cancer

Katsumata N. Lancet Oncol 2013;14(10): 2014.

Chemotherapy regimen

Taxol
Ifosfamide
Cis Platinum

Taxol
Cis Platinum

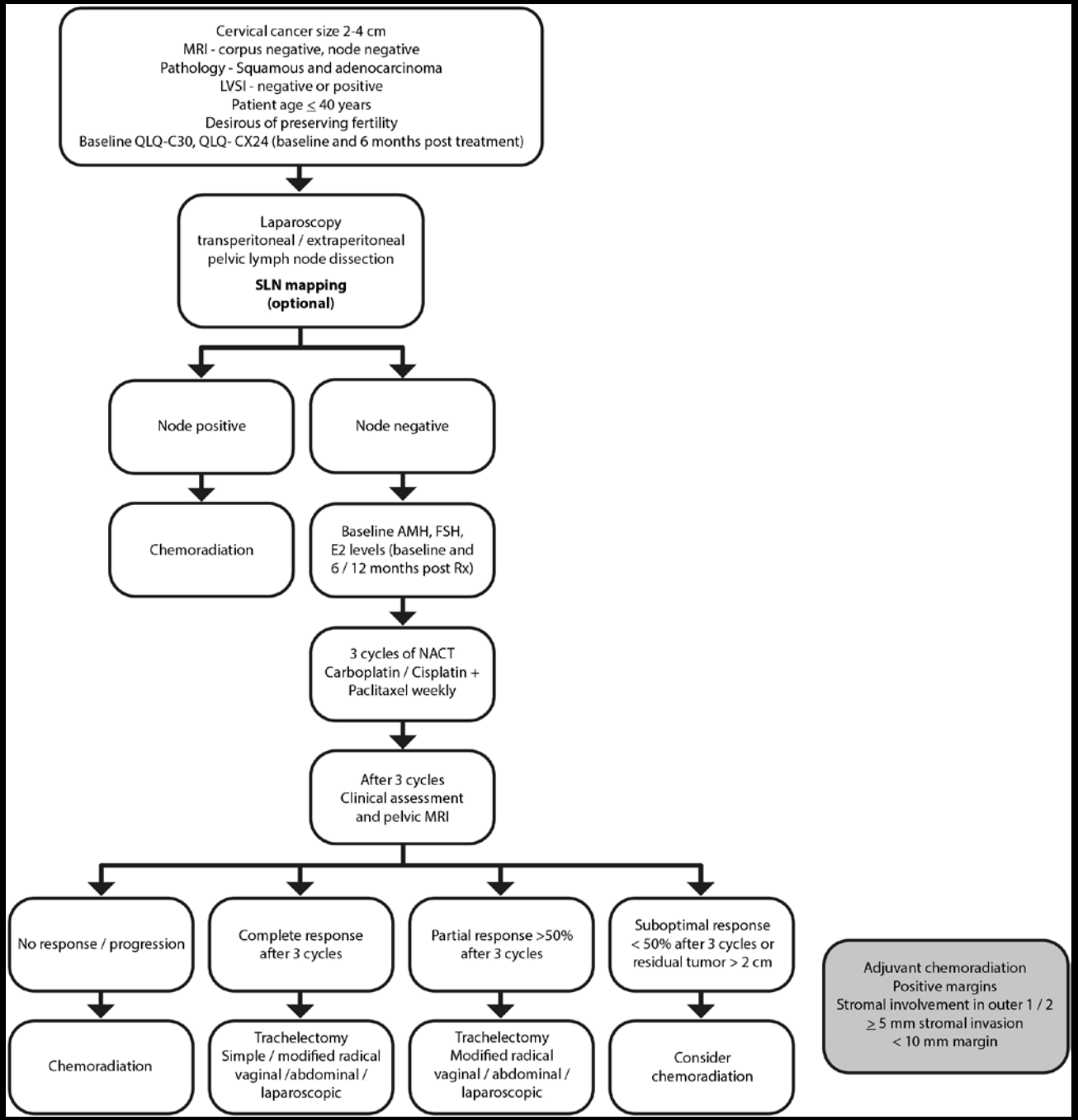
Taxol
Carbo Platinum

Dose Dense Taxol-Carbo
- Weekly TC
- Weekly Taxol/3W Carbo

Optimal chemotherapy regimen

- Adding GnRHa during chemo ?
  - Breast cancer data suggest a benefit of adding goserelin with chemotherapy
  - Protect against ovarian failure
  - Reduce the risk of early menopause
  - Improve prospects for fertility

Moore HCF. N Engl J Med 2015;372:923-32.


Cervical cancer size 2-4 cm
MRI - corpus negative, node negative
Pathology - Squamous and adenocarcinoma
LVSI - negative or positive
Patient age ≤ 40 years
Desirous of preserving fertility
Baseline QLQ-C30, QLQ- CX24 (baseline and 6 months post treatment)
Laparoscopy
transperitoneal / extraperitoneal
pelvic lymph node dissection
SLN mapping
(optional)
Node positive
Node negative
Chemoradiation
Baseline AMH, FSH,
E2 levels (baseline and
6 / 12 months post Rx)
3 cycles of NACT
Carboplatin / Cisplatin +
Paclitaxel weekly
After 3 cycles
Clinical assessment
and pelvic MRI
No response / progression
Complete response
after 3 cycles
Partial response >50%
after 3 cycles
Suboptimal response
< 50% after 3 cycles or
residual tumor > 2 cm
Chemoradiation
Trachelectomy
Simple / modified radical
vaginal /abdominal /
laparoscopic
Trachelectomy
Modified radical
vaginal / abdominal /
laparoscopic
Consider
chemoradiation
Adjuvant chemoradiation
Positive margins
Stromal involvement in outer 1 / 2
≥ 5 mm stromal invasion
< 10 mm margin

Outcome measures

- **Primary end point**
  - **Successful fertility preservation defined as intact uterine corpus with no adjuvant XRT**

- **Secondary end points**
  - **Response rates to chemotherapy**
  - **Toxicity**
  - **Proportion requiring trimodality treatment**
  - **QoL indices / Ovarian function indices**
  - **3 and 5 year disease free survival**

Phase II: Sample Size