Princess Margaret Consortium

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

DUTCH GOG
Dutch Gynaecological Oncology Group

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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

Dre Marie Plante

Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F)

Dr Frédéric Amant

Background

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

Background

- **Management options for patients with larger size lesions**
  - **Upfront Radical Trachelectomy**
  - **NACT followed by fertility-preserving surgery (FPS)**

Abdominal Trachelectomy

- ART can be performed in **larger size lesions**
- **Wider parametria** and **more radical** surgery can be obtained with ART
  - Increased surgical morbidity
  - Reduced fertility outcome

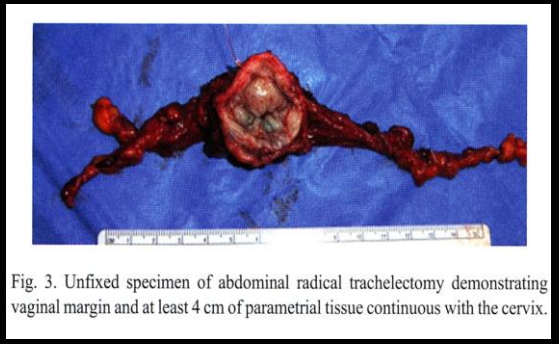
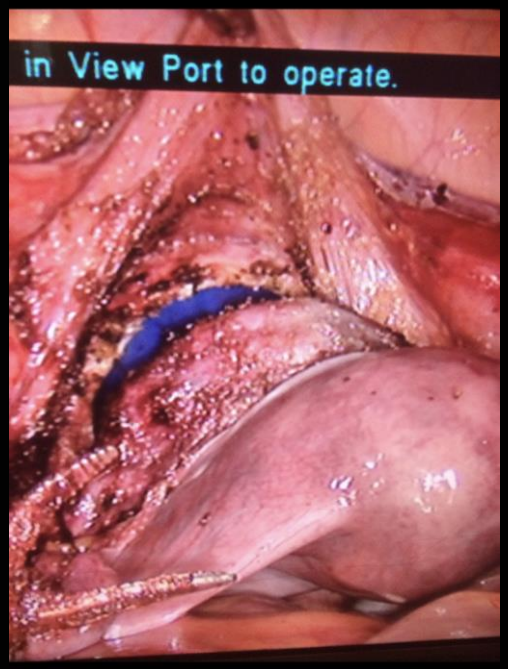
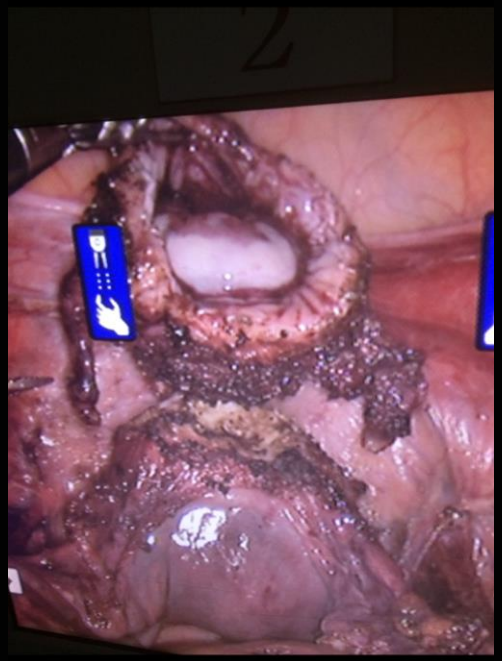


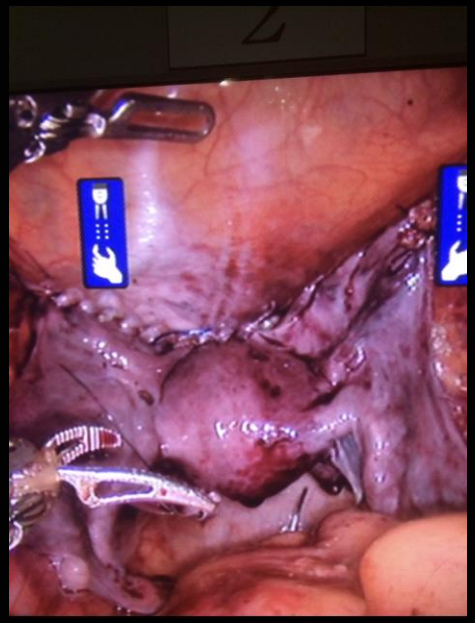
Fig. 3. Unfixed specimen of abdominal radical trachelectomy demonstrating vaginal margin and at least 4 cm of parametrial tissue continuous with the cervix.

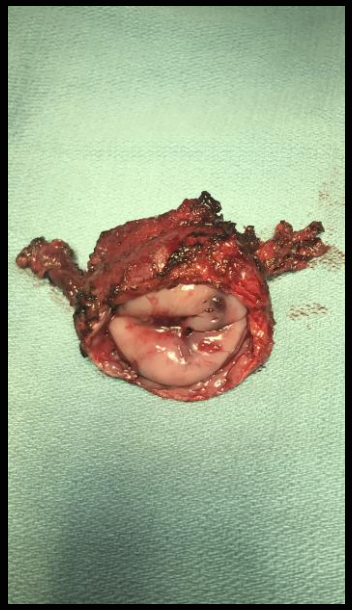
Robotic Trachelectomy

LACC TRIAL ?????









Courtesy; Dr Taymaa May

Upfront Trachelectomy

- Associated with high rates of **adjuvant radiation therapy**
- Huge impact
  - Fertility
  - Ovarian function
  - QoL

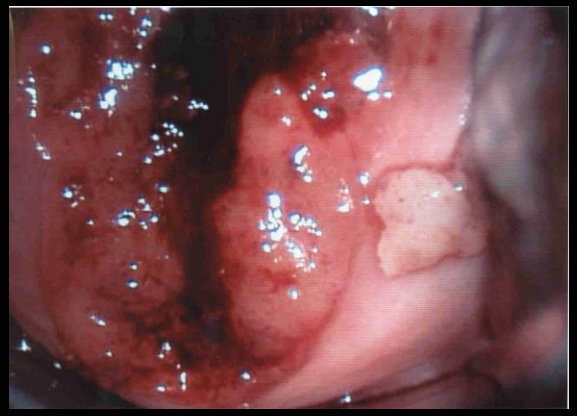
Indications for adjuvant RT

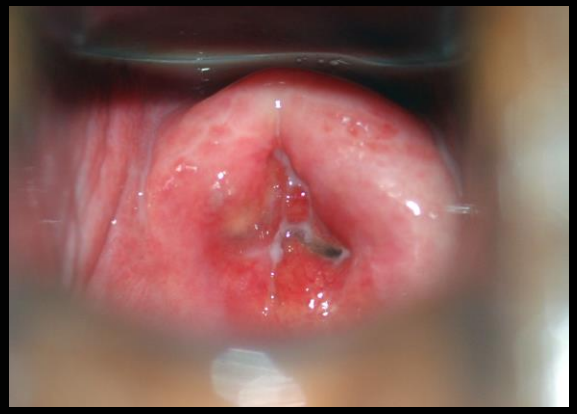
LVSI	Stromal Invasion	Tumor Size
Positive	Deep 1/3	Any
Positive	Middle 1/3	> 2
Negative	Superficial 1/3	> 5
Negative	Deep or Middle 1/3	> 4

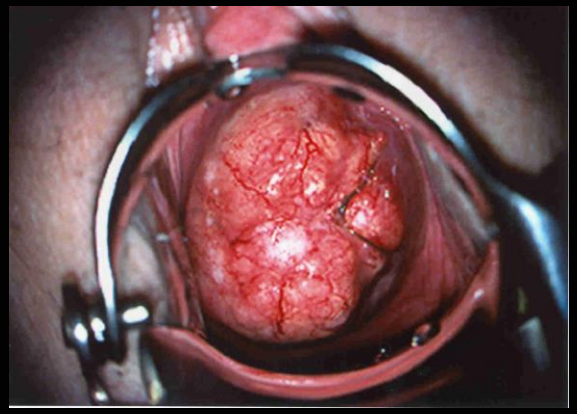
GOG 92: Sedlis criteria (needing 2 or more of these factors)

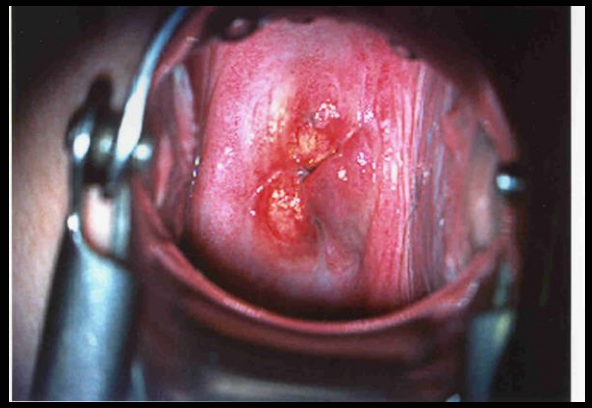
- LVSI involvement
- Deep stromal invasion (middle or deep third)
- Size > 4 cm

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%)

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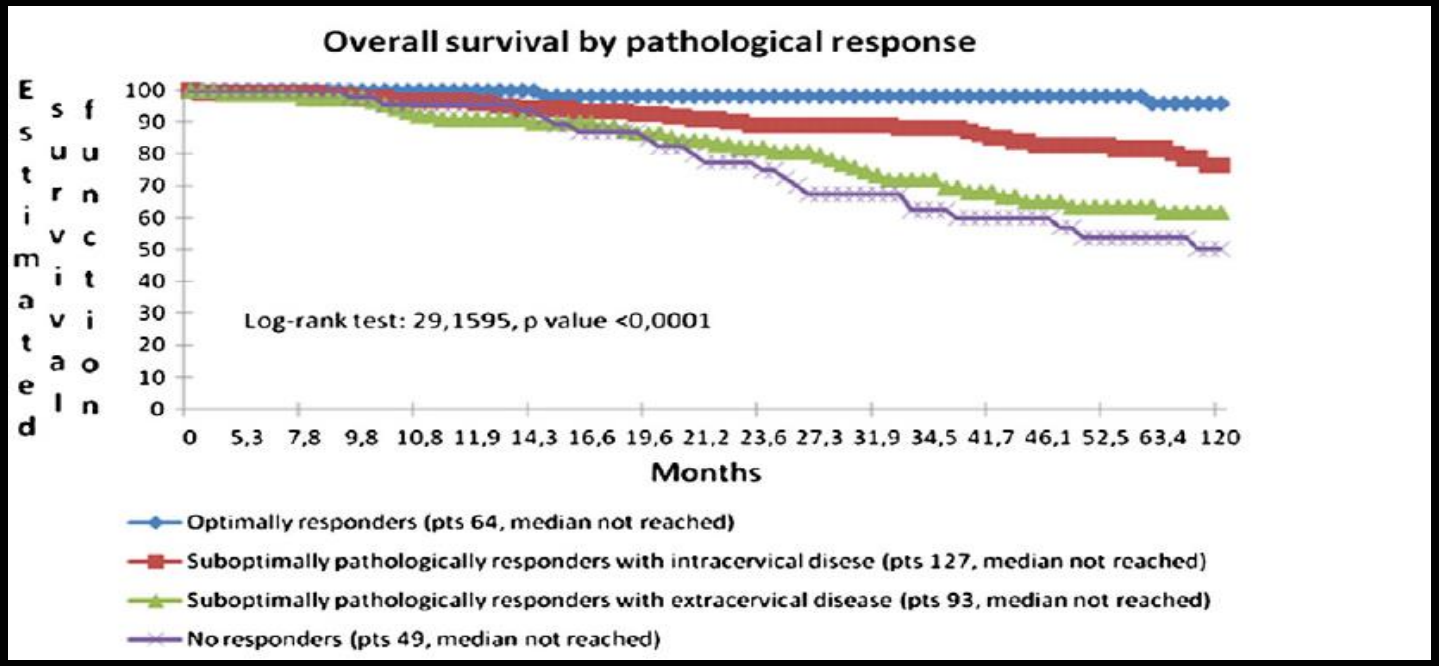
Pathological response to NACT & Survival



- Multicentre Italian trial
- Retrospective review 333 pts IB2/IIB
- Median FU 66m
- NACT- rad hyst/PLND
- Overall RR 86%, optimal 20%

Gadducci et al Gynecol Oncol 2013

Chemotherapy regimen

Italian Q 3 weeks x 3	Taxol 175 mg/m2	Ifosfamide 5g/m2	Cisplatin 75 mg/m2
"Ovarian" Q 3 weeks x 3	Taxol 175 mg/m2		Carbo AUC 6
Dose dense Weekly x 9	Taxol 80 mg/m2		Carbo AUC 2
"Belgian" Dose dense Weekly x 9	Taxol 60 mg/m2 No alopecia		Carbo AUC 2.7
Prague regimen Q 10d x 3		Ifosfamide 2g/m2 Squamous	Cisplatin 75 mg/m2
Prague regimen Q 10d x 3		Adriamycin 35mg/m2 Adenoca	Cisplatin 75 mg/m2

9 weeks = 63 days

EORTC 55994 regimen

NACT and Fertility Sparing

- Small retrospective studies
- Lack of standardization
  - Timing of LN staging
  - Type of fertility preserving surgery
  - Choice of chemotherapy regimen

CONTESSA TRIAL

Specific Hypothesis

- Neoadjuvant chemotherapy (NACT) in node-negative women with stage IB1 (2-4 cm) cervical cancer will enable fertility preserving surgery without compromising oncologic outcome in good chemo-responders

Primary Objective #1

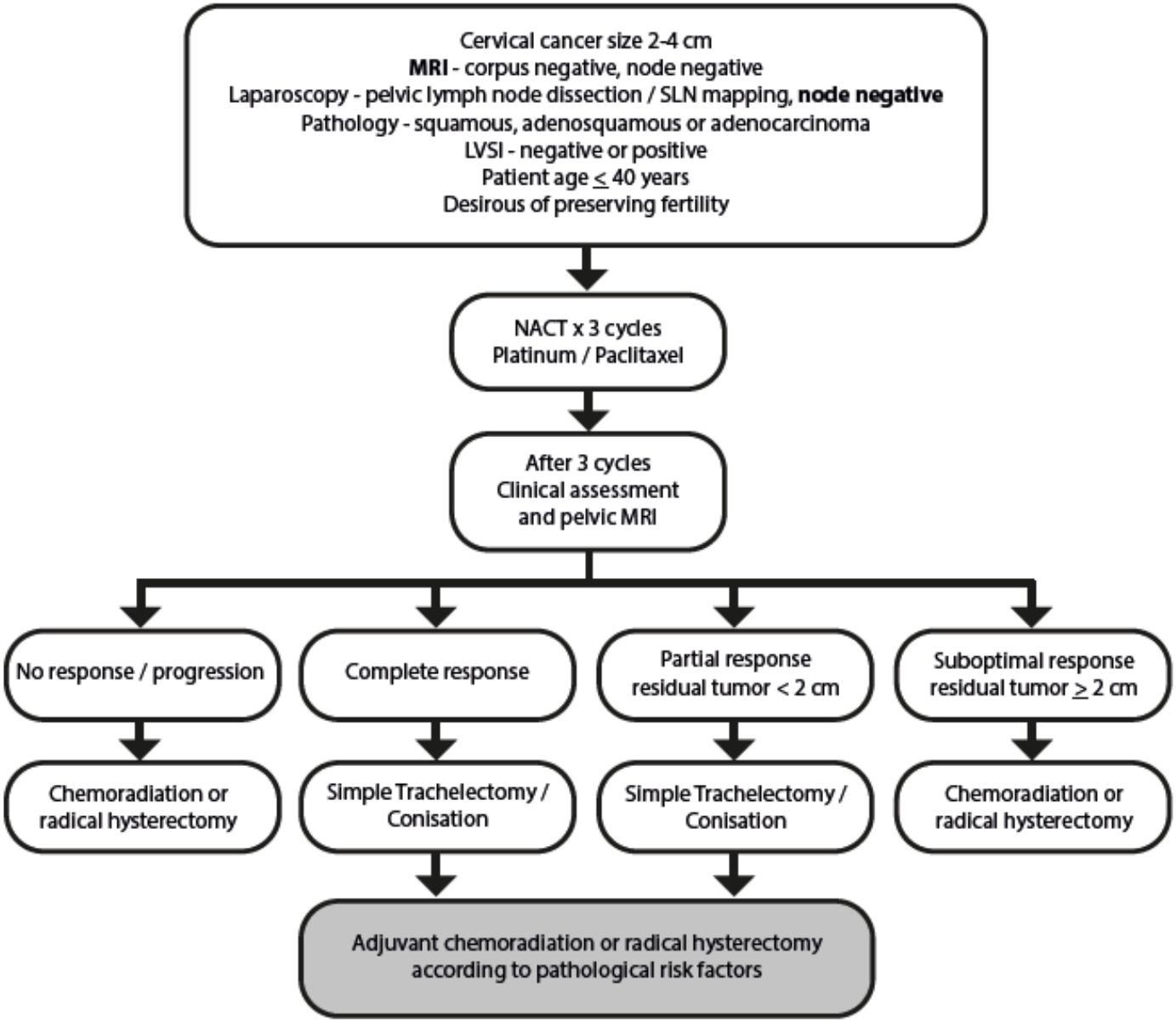
- To evaluate the safety of NACT in women with node negative, stage IB1 cervical cancer with lesions measuring 2-4 cm

Primary Objective #2

- To evaluate the **rate of fertility preserving surgery** following neoadjuvant chemotherapy (NACT)

Secondary Objectives

- Chemotherapy related adverse events / safety
- Surgical complication rate of FPS
- Requirement for adjuvant radiation therapy (trimodality treatment)
- Requirement for definitive hysterectomy
- Quality of Life
- Ovarian function, rates of pregnancy and obstetrical outcomes


Cervical cancer size 2-4 cm
MRI - corpus negative, node negative
Laparoscopy - pelvic lymph node dissection / SLN mapping, node negative
Pathology - squamous, adenosquamous or adenocarcinoma
LVSI - negative or positive
Patient age ≤ 40 years
Desirous of preserving fertility
NACT x 3 cycles
Platinum / Paclitaxel
After 3 cycles
Clinical assessment
and pelvic MRI
No response / progression
Complete response
Partial response
residual tumor < 2 cm
Suboptimal response
residual tumor ≥ 2 cm
Chemoradiation or
radical hysterectomy
Simple Trachelectomy /
Conisation
Simple Trachelectomy /
Conisation
Chemoradiation or
radical hysterectomy
Adjuvant chemoradiation or radical hysterectomy
according to pathological risk factors

Primary endpoints

- Recurrence rate/PFS at 3 years (#1)
- Intact functional uterus following NACT and FPS (#2)

Statistical analysis

- Phase II study
- Prospective, multi-center, international trial

Statistics : PRELIMINARY

- **Sample size was calculated based on the efficacy outcome**
  - **Based on the hypothesis that 70% of patients will proceed to FSS following NACT**
  - **61 evaluable patients will provide a two-sided 96% CI**
  - **Up to 75 patients may be accrued to reach 61 evaluable patients**
    - **Drop out rate, need for adjuvant RT**

Statistics : PRELIMINARY

- Considering the **safety endpoint** based on the NACT completion rate
  - **An interim analysis after 24 patients** accrued will be performed
  - If **less than 13 ptes** are able to complete NACT, trial will be **terminated**
  - The trial will be considered **safe if >37/61** are able to complete NACT

Statistics : PRELIMINARY

- The 2-year recurrence rate will also be monitored
  - Monitoring will start after 10 patients are accrued and up to 30 evaluable patients
  - The trial will be considered unsafe if there is a 70% probability that the 2-year recurrence rate is greater than 15%

Statistics : PRELIMINARY

Stopping Rules

Number of evaluable patients	Number of 2-year recurrence	Stop the trial
10	>=3	Yes
15	>=4	Yes
20	>=5	Yes
25	>=6	Yes
30	>=7	Yes

Translational research

- Assessment of **tumor response**
  - Circulating tumor DNA (ctDNA)
  - Serial blood sample collection
    - Baseline
    - Chemotherapy cycle 2
    - Surgery
    - 3-month follow-up visit

Funding

- PMH Consortium
  - Per case funding for Canadian patients
  - Data collection and data monitoring
- Netherlands (CGOA/NCI)
  - Per case funding for Dutch patients
- Other groups
  - Will have to secure own funding

Summary

- Feasable study
- Count on international collaboration
- Will provide solid data as to the safety of this approach and standardize the procedure