

# **Neoadjuvant chemotherapy and surgery in cervical cancer**

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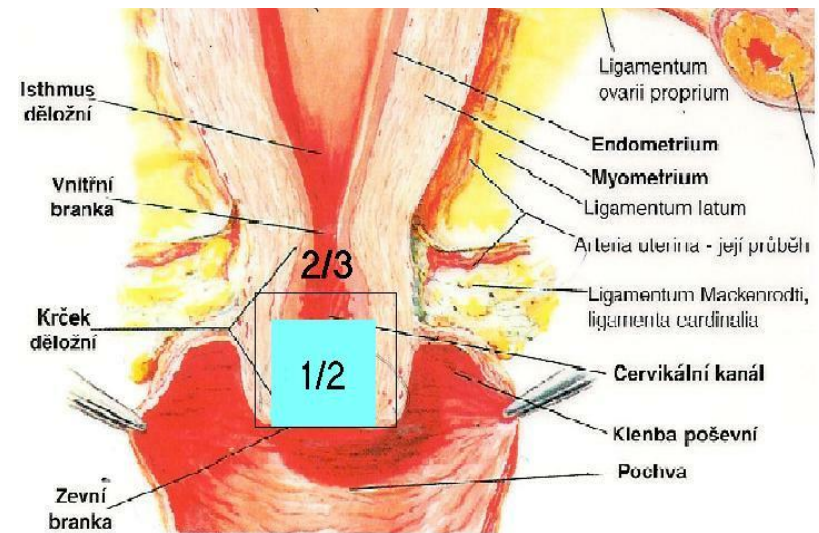
## Part I - Neuroendocrine ca – NAC + surgery

### Histopathology

- SCC
- AC
- ASC
- **Neuroendocrine ca**

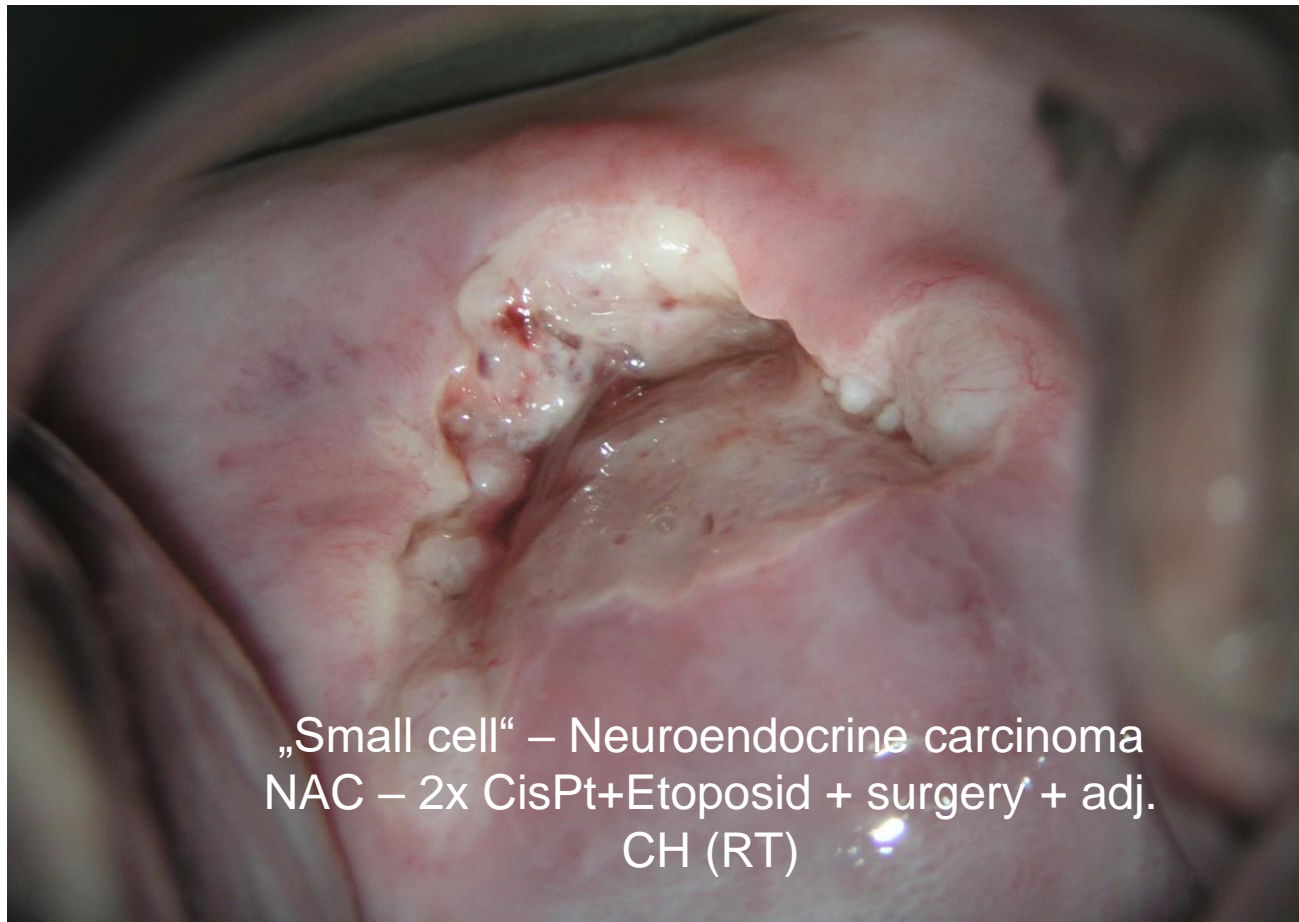
„**MRI**“ volumometry

„**Ultrasound volumometry**“



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## **NAC – neuroendocrine cervical cancer (2000-2015)**

**2x NAC ... RH ... 2x CH +/- radiotherapy**

**(Day 1 - CisPt 75mg/m<sup>2</sup>, Day 1-3 Etoposid 120mg/m<sup>2</sup>)**

- IB1 - 12x - 8x N0 4xN+ (**38/5**, 36/1, 29/1, 32/2) ... 3 DOD
- IB2 - 6x - 3x N0 3xN+ (**36/3**, **43/2**, **36/33**) ... 3 DOD

**After NAC -**

**11/N0 ... 2 DOD - 82% CR**

**7/ N+ ... 4 DOD - 43% CR**

**67%**

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**GCIG - „no standard treatment guideline has been established“  
(GOG ... GCIG)**

**A/ Early Stage (I-IIA)  $\leq$  4cm - RH + lymphad....CH (Cis+Etoposid) +- RT  
B/  $\geq$  4cm - NAC + RH + lymphad....CH (Cis+Etoposid) +- RT**

- Role of NAC  $\leq$  4cm ?**
- Role radiotherapy ?**
- Less toxic chemotherapy ? New target therapy ?**

**? Randomised trial ?**

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## Important literature:

- Satoh T, et al.: Gynecologic Cancer InterGroup (**GCIG**) consensus review for small cell carcinoma of the cervix, Int J Gynecol Cancer, 24 (**2014**) S 102-8
- Gardner GJ et al.: Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (**SGO**) clinical document, Gynecol. Oncol. 112 (**2011**) 190-198
- Ishikawa M, et al.: Prognostic factors and optimal therapy for stage I-II neuroendocrine carcinomas of the uterine cervix: A multi- center retrospective study, Gynecol. Oncol. 148 (**2018**) 139-146
- Zivanovic O et al.: Small cell neuroendocrine carcinoma of the cervix: analysis of outcome, recurrence pattern and the impact of platinum – based combination chemotherapy, Gynecol. Oncol. 112 (**2009**) 590-593
- Gadducci A. et al.: Neuroendocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists, Gynecol. Oncol. 144 (**2017**) 637-646

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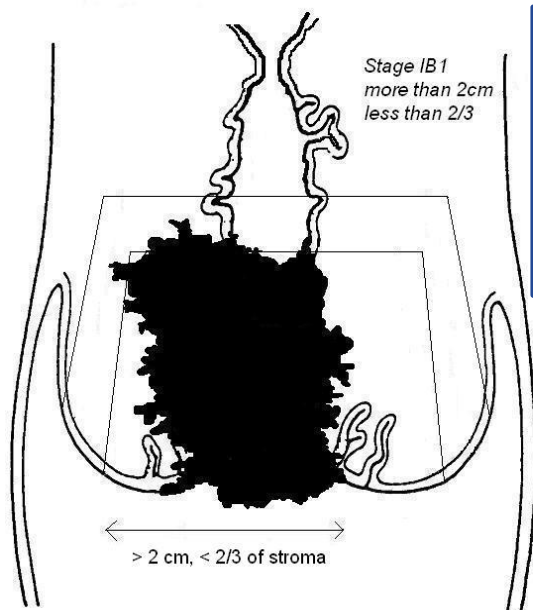
## Part 2 – Fertility sparing surgery - NAC

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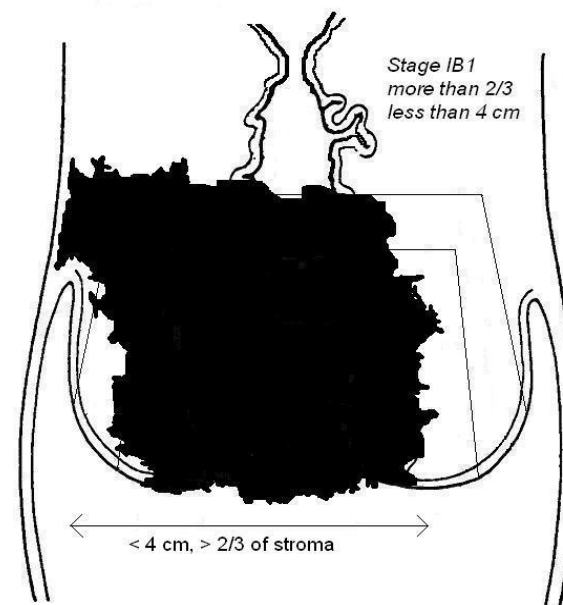


Early stage cervical cancers which do not fulfill the condition of  
fertility sparing surgery

Radical hysterectomy x radical abdominal trachelectomy x NAC +  
fertility sparing surgery?



10-18%  
N  
positive



25-40%  
N  
positive



## **Early stage cervical cancers which do not fulfill the condition of fertility sparing surgery**

**Ib1 more than 20 mm +**

**Ib1 infiltration less than 2/3 stromal volumometry**

### **NAC a fertility sparing surgery???**

**Maneo et al. 2004 – IGCS**

**Rob et al. 2005 – IV. Cervical Cancer Conference, Houston**

**Plante et al. 2006 - Gynecol Oncol 101: 367- 70**

**Maneo et. al. 2008 - Gynecol Oncol 111:438 - 43**

**Robova et al. 2008 – Int J Gynecol Cancer 18(6):1367- 71**

**Robova H, Rob L et al. 2014 - Gynecol Oncol 135:213 - 16**

**Salihi R, Vergote I. et al. 2015 – Gynecol Oncol 139:447 - 51**

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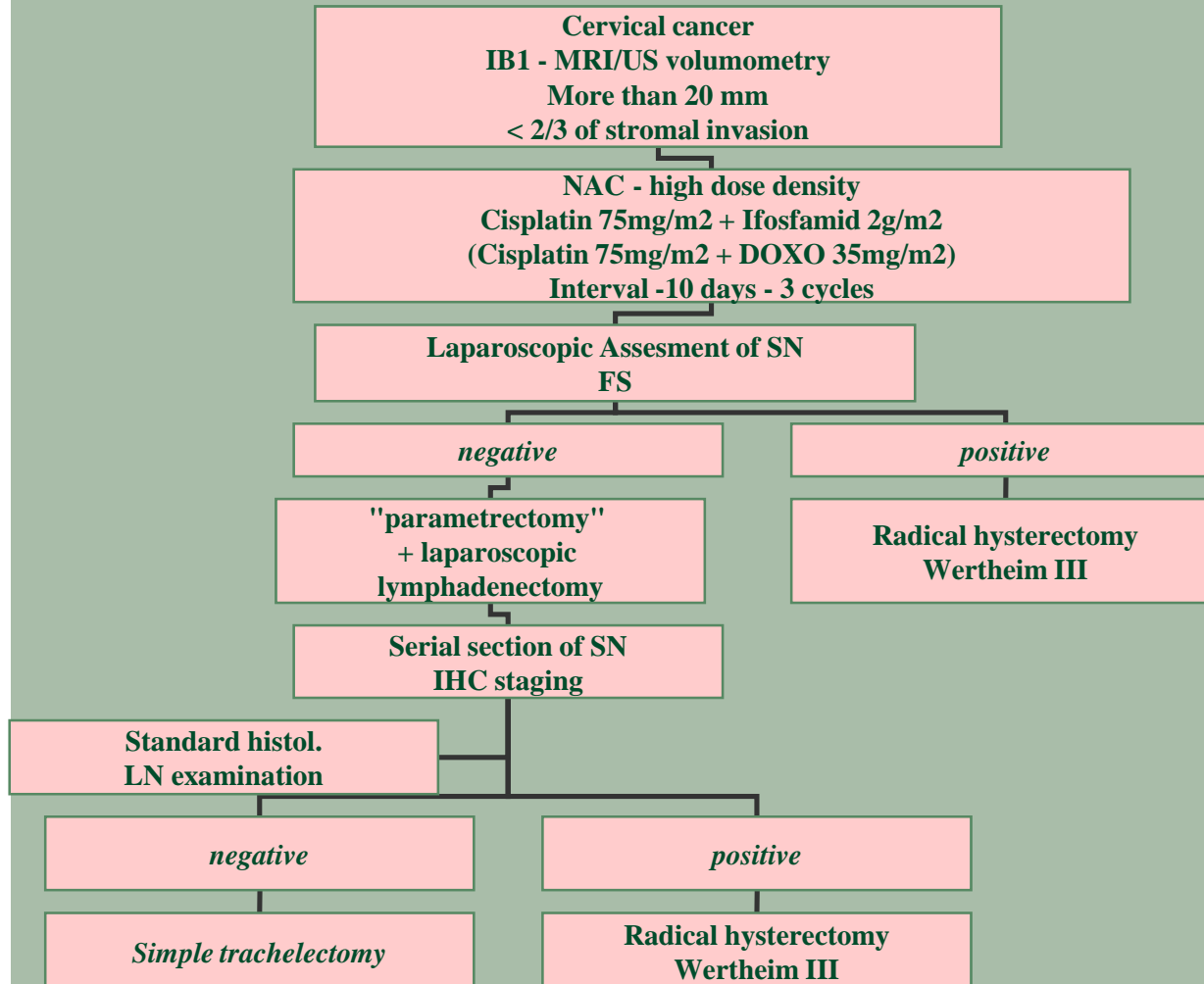
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**GYNECOLOGIC  
CANCER INTERGROUP**

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

## LAP 3/NAC - SLNM and conservative surgery (1/2005)



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In time of diagnosis – Colpo + TU volumetry

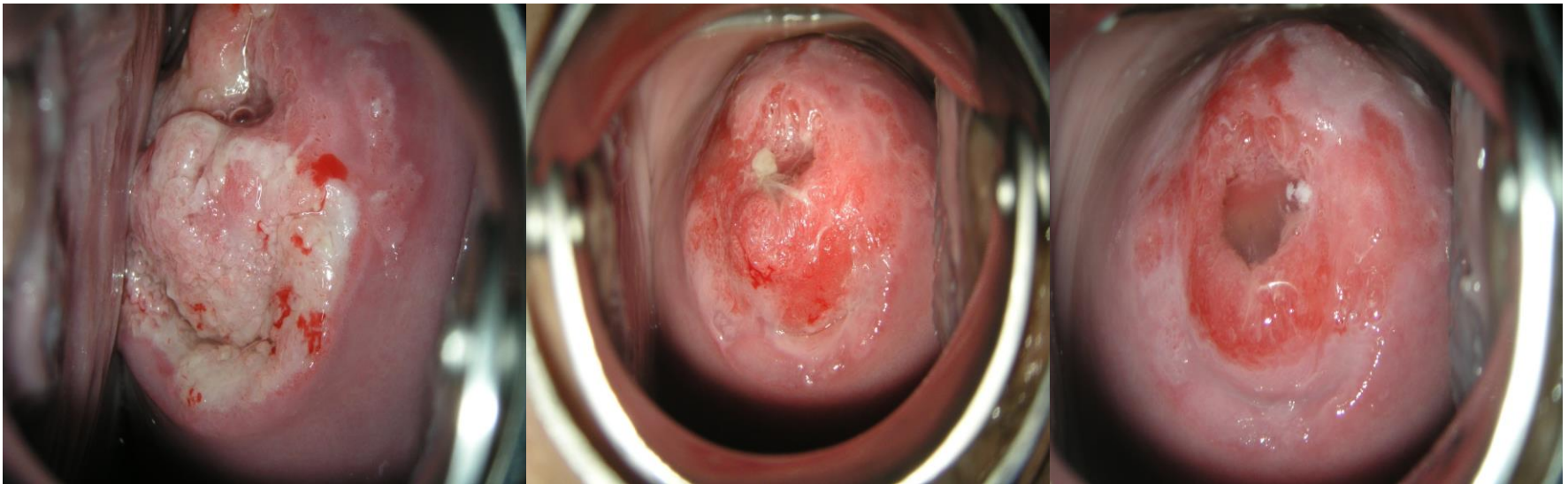


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Before chemo ..... before 2nd NAC ..... after 3rd NAC



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## **LAP 3 – high-dose density chemotherapy**

### **Prague protocol -**

- **CisPt 75mg/m<sup>2</sup> + Ifosfamid 2g/m<sup>2</sup> - squamous cell cancer**
- **CisPt 75mg/m<sup>2</sup> + Adriamycin 35mg/m<sup>2</sup> - adenocarcinoma**
  - interval 10 days
  - 3 cycles chemotherapy (dose dense)
- **Toxicity**  
haematological – grade 3 neutropenia 17.9% (no other grade 3 and 4)

**X TIP (paclitaxel, ifosfamid, cisplatin) ... (Milan, Monza, Rome)**  
**paclitaxel + carboplatin – dose dense (Leuven)**  
**paclitaxel + carboplatin - weekly (Leuven)**

## **LAP 3 protocol (2005 – 2014)**

**– high-dose density chemotherapy + fertility sparing**

- 2005-2014 **32 women** (28 nulliparous)
- Mean age 28.6 years (15-34 years)
- 17 (53.1%) squamous cell ca
- 15 (46.9%) adenocarcinoma
- 24 (75%) FIGO IB1 (MRI + US volumometry)
- 8 (25%) FIGO IB2 (MRI + US volumometry)

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## LAP 3 – Oncology outcome (2005 – 2014) – follow up 12/2017

- 7 women (21.9%) - no residual disease
  - 11 women (34.3%) - microscopic (less than 3 mm)
  - 14 women (43.8%) - macroscopic residual disease – suboptimal - CR+PR – 100%
- Optimal  
56.2%
- 22 women (68.8%) - fertility was spared
  - 4 women (12.5%) – underwent immediate radical hysterectomy for positive SLN on frozen section
  - 6 women (18.7%) – underwent radical hysterectomy for close/ positive margins (4) or patient's decision (2)
  - **Recurrence rate 4/22 women (18.2%)**
    - 3 local recurrences (2 AC, 1 SCC) + 1 distant recurrence (SCC)\*
  - **Mortality rate 2/22 women (9.1%) - both SCC**
- \* 6 weeks after successful pregnancy – metastasis in the ovary



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## LAP 3 – pregnancy outcome (2005 – 2014) – follow up 12/2017

- Fertility was spared in 22 women
    - 4 women – no plan to be pregnant ( 18.2 %)
    - **18 women plan pregnancy ( 81.8 %)**
  - **13 women (59.1%) became pregnant = pregnancy rate 72.2%**
  - 11 women delivered **13 babies**
    - 5 premature delivery (PROM) – 24w, 28w (15.4%),  
34w, 35w, 36w (23.1%)
    - 8 term delivery (37-41w) – (61.5%)
    - 2 missed abortion in I.st trimester
    - 1 women miscarried 2x in second trimester (PROM)
- 2x IUI, 1x IVF (17.6%)**  
**(1 women – 3x IVF unsuccessful)**

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## Questions – NAC + fertility sparing

- Which type of chemotherapy TIP/TAP  
dose dense chemotherapy - CarboPt + paclitaxel ?  
weekly – CarboPt + paclitaxel ?
- Can anything reduce recurrence rate and mortality?
- Adjuvant chemotherapy in women with residual disease??
- **Neoadjuvant chemotherapy + LAP + vaginal trachelectomy  
x abdominal (robotic) radical C1/C2 trachelectomy??**

## Conclusions

- Any type of fertility sparing surgery in cervical cancer bigger than 2 cm is **still an experimental method**
- Women must be informed about higher risk of recurrence
- Favorable method of fertility-sparing surgery would be method that give women good oncology results and the best chance for pregnancy

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## Review – NAC + fertility sparing

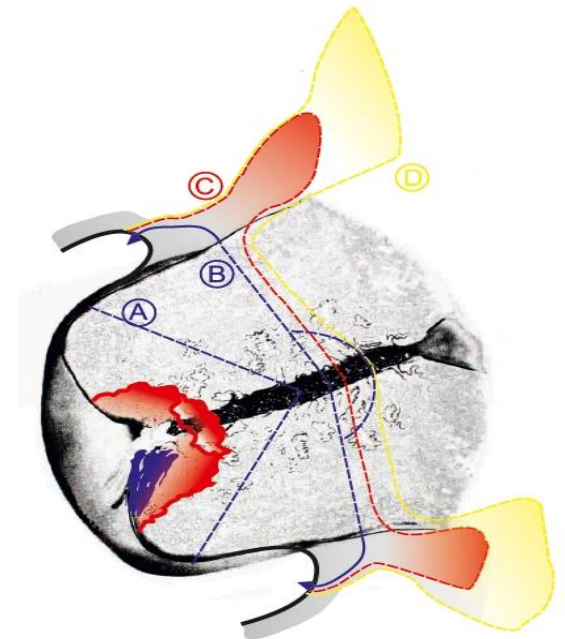
Rob L. et al.: Expert Rev Anticancer Ther. 2010 Jul;10(7):1101-14

Rob L. et al.: Lancet Oncol. 2011 Feb;12(2):192-200

Robova H. et al.: Curr Oncol Rep. 2015;17(5):446 -50

Salihi R. et al.: Gynecology Oncology 2015;139: 447-451

Bontivegna et al. Lancet Oncol. 2016, 17, 240-53

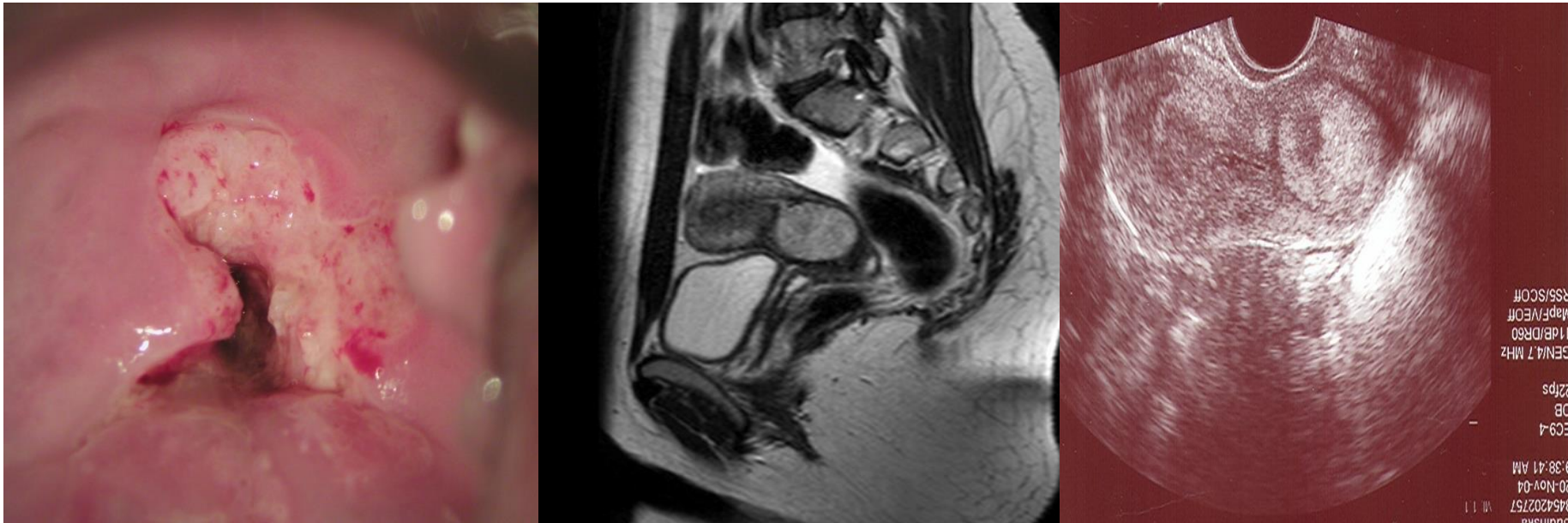


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## Part 3 – „bulky“ tumour, IB1, IB2, IIB - NAC + radical surgery ?



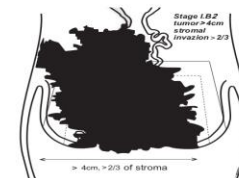
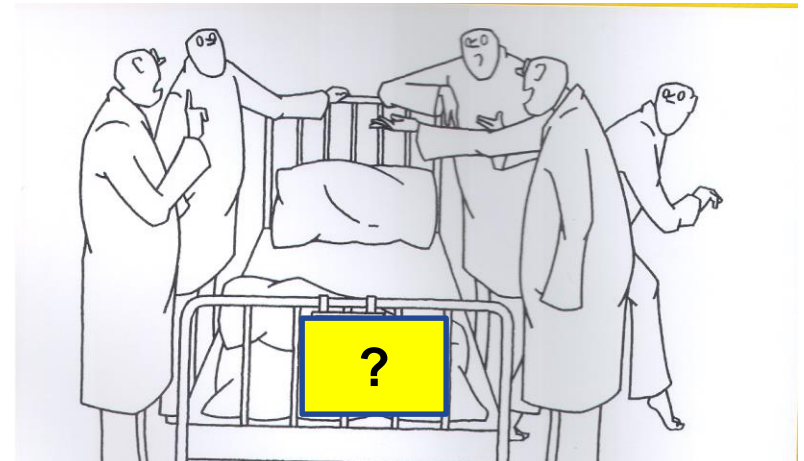
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## „Bulky“ cervical cancer (IB2) evidence based approach in 2018?

- Radical surgery + adj. RT ?
- Chemoradiotherapy ?
- Neoadjuvant chemotherapy followed by radical surgery ?



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## Neoadjuvant chemotherapy followed by radical surgery

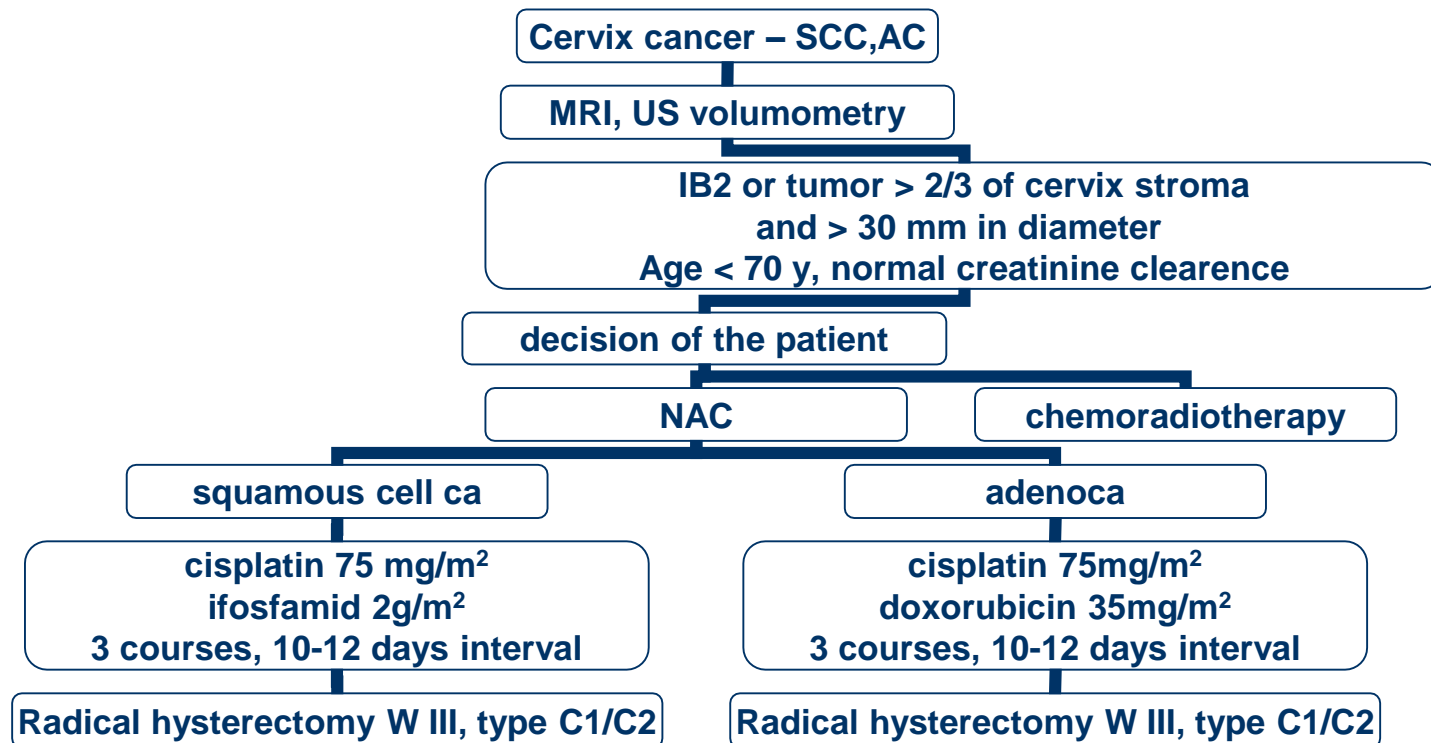
- Tumor size reduction – (shrink the tumor)
  - Increase operability, „safety“ free margins, „**make surgery easier**“
  - **!!! Patient selection - free „anterior-ventral“ paracervix!!!**
- Treatment of small metastatic and micrometastatic disease
  - Prevent distant recurrences?
  - Decrease number of positive lymph nodes.
- Excluding of radiotherapy – **improvement of QOL** – especially in young women.
- Chemotherapy + Surgery +- Chemotherapy
  - **Improve QOL**



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## NAC + RH – Prague protocol



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## NAC followed by radical surgery – patient characteristic Protocol CervNAC I – 1998-2009 ..2010 – 12/2015

### 151 women (1/1998- 12/2009)

IB2\* / locally advanced - 119 women\* (78.8%)  
IB1 (3-4 cm, fully infiltrated) - 32 women (21.2%)

Squamous cell ca - 133 women (88.1%)  
Adenocarcinoma - 16 women (10.6%)  
Other - 2 women (1.3%)

Median age 45.7 year (Range 20-70)

RH + lymphadenectomy – 142 women (94.0%)

ChemoRT (Non responder/ PD) – 9 women (6%)

### 80 women (1/2010-12/2015)

- 68 women\* (85%)  
- 12 women (15%)

- 62 women (77.5%)  
-16 women (20%)  
- 2 women (2.5%)

44.2 (Range 24-65)

79 women (99%)

1 women (1%)

**Robova H., Rob L., Halaska MJ et al. High – dose density neoadjuvant chemotherapy in bulky IB cervical cancer, *Gynecol. Oncol* 2013, 128 , p. 49-53**

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## **NAC – Prague protocol**

### **squamous**

Cisplatin 75 mg/m<sup>2</sup>  
+ Ifosfamid 2g/m<sup>2</sup> (no more than 3g)

**Interval 10 – 12 days**

cumulative dose – 3 week

CisPt 225mg/m<sup>2</sup>, Ifo- 6g/m<sup>2</sup>)

### **adenocarcinoma**

Cisplatin 75 mg/m<sup>2</sup>  
+ doxorubicin 35mg/m<sup>2</sup>

**Interval 10 – 12 days**

cumulative dose – 3 week

CisPt 225mg/m<sup>2</sup>, Doxo-105mg/m<sup>2</sup>

Gr 3,4 toxicity

Neutropenia: 11 (7.3%), Trombocytopenia: 2 (1.3%), Anemia: 0

Encephalopathy (ifosfamide): 2 (1.3%), Ototoxicity: 1 (0.7%)

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## Protocol CervNAC I – 1998-2009 ..2010 – 12/2015

- Reduction of tumor volume (231 patients)
  - no residual disease- 31 women (13.4%)
  - reduction more than 50%- 159 women (68.8%)
  - reduction less than 50 %- 31 women (13.4%)
  - No response, progression- 10 women (4.3%)
- Lymph nodes
  - positive lymph nodes- 40/221 women (18.1%)

**Primary surgery - 1988-1998, IB2–38/105 (36.2%) positive LN**

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## Protocol CervNAC I – 1998-2009 ..2010– 12/2015

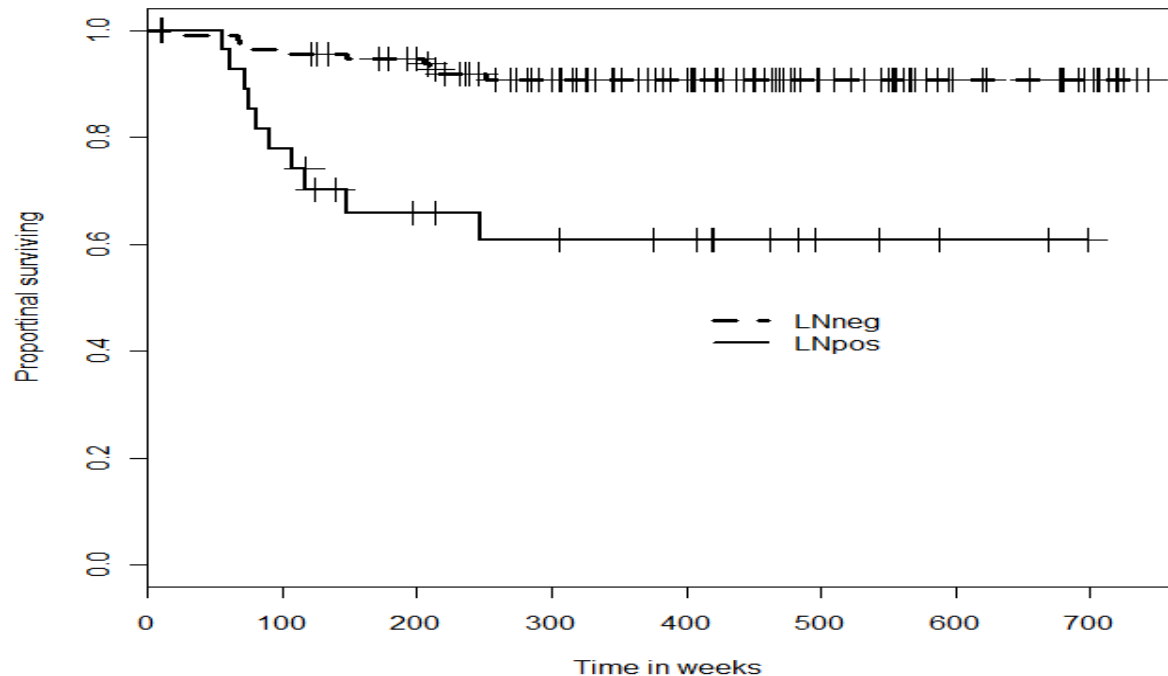
- **Without treatment** – 36 women (16.3%)
  - no or microscopic residual disease
- **Adjuvant chemotherapy** - 131 women (59.3%)
  - 3 cycles of the same chemotherapy in interval 21 days
- **Adjuvant radiotherapy** – 54 women (**24.4%**)
  - positive lymph nodes and/or minimal tumor volume regression
- **NAC + surgery** 1998-2009                      **NAC + surgery** 2010-2015
  - recurrence rate – 20/142(14.1%)                      8/79 (10.1%)
  - died of disease – 19/142(13.4%)                      7/79 ( 8.9%)
- **NAC + chemoradiotherapy**                      **NAC + chemoradiotherapy** 2010-2015
  - recurrence rate – 6/9 (66.7%)                      0/1 (0%)
  - died of disease - 6/9 (66.7%)                      0/1 (0%)

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## Disease specific survival – lymph node status

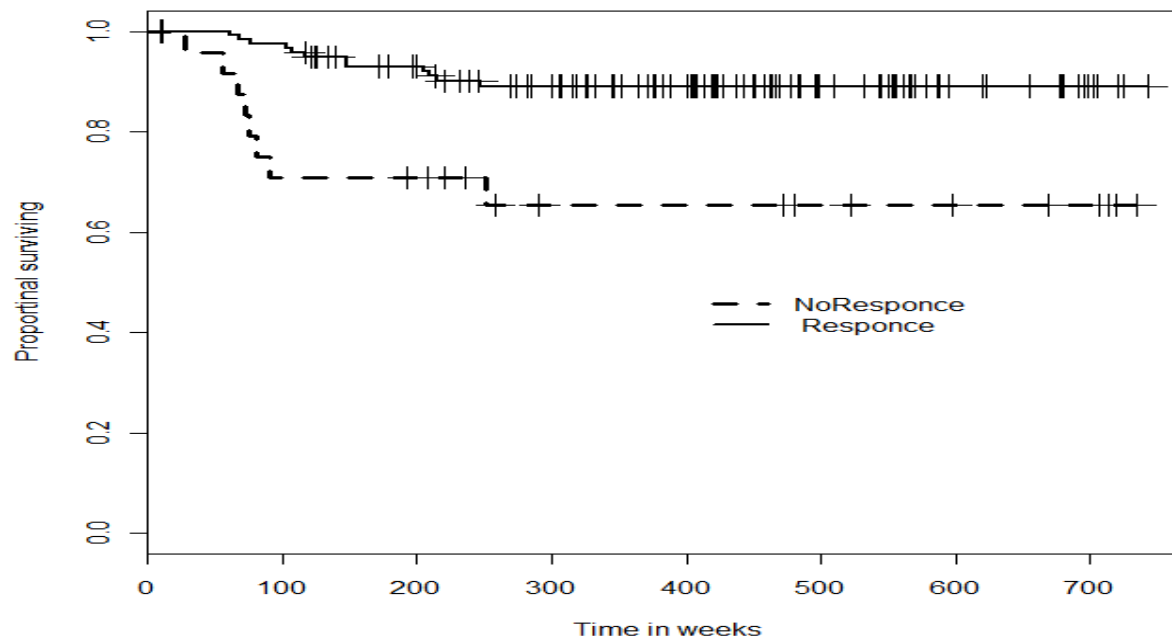


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## Disease specific survival – response to chemotherapy



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- **NAC + radical surgery – Prague experience**
- NAC- dose dense - reduce tumor volume, LVSI and reduce positive number of lymph nodes
- NAC - dose dense - reduced necessity of radiotherapy in 75% – improved QOL in young women
- High-dose density chemotherapy followed by „good“ radical surgery is feasible and safe treatment methods in „bulky“ cervical cancer in young women
- NAC followed by radical surgery improved the clinical outcome of patients with bulky disease when compared with primary surgery
- 3 and 5-year survival is comparable with precise chemoradiotherapy in bulky IB cervical cancer

## **Crucial future question** - patients selection for NAC

- optimal chemotherapeutic regiment for NAC (carbo x cisPt + xxx)
- optimal dose dense, optimal time to surgery
- the role of adjuvant chemotherapy

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## **CONCLUSION**

- 1/ NAC is important part of management neuroendocrine cervical ca
- 2/ NAC and fertility sparing surgery - chance to preserve fertility in women with Ib1 cervical cancers bigger than 20 mm
- 3/ High dose density NAC followed by good radical surgery seem to be feasible for „bulky“ cervical cancer
  - NAC – reduce of tumour volume and significant **decrease the positive lymph nodes** (36%x18%)
  - NAC – significant **reduce adjuvant postoperative radiotherapy -QOL**
  - 5 year survival in patients which underwent surgery in our study was 85%(in our historic „control group“ – SURGERY+RT“ was 5 year survival 69%)

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## ***NAC – review***

**Friedlander M et al.:** Cervical carcinoma: a drug-responsive tumor – experience with combined cisplatin, Vinblastin, and Bleomycin therapy. *Gynecologic Oncology* **1983, 16 (2): 275-81**

**Tierney JF et al.:** Concomitant and neoadjuvant chemotherapy for cervical cancer. *Clinical Oncology*, **2008, 20 (6): 401-416**

**Rydzewska L et al.:** Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer (**Cochrane Database Syst Rev. 2012, 12:CD007406**)

**Lampresa M et al.:** Neoadjuvant chemotherapy in cervical cancer: an update. *Expert Rev Anticancer Ther.* **2015, 15(10), 1171-1181**

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