

# **Update on Neoadjuvant Chemotherapy (NACT) in Cervical Cancer**



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# NACT in Cervical Cancer

**NACT**

**Stage**  
**-IB2**  
**-IIA $>4$ cm**  
**-IIB**

**Stage 1B1**  
**Fertility**  
**Sparing**

**RH**

**Conization**

# Fertility-Preserving Surgery in Cervical Cancer: Oncologic Outcome

- VRT
  - < than 2 cm - 2.9%
  - > than 2 cm - 20.8%
  - total - 4.7%
- ART
  - < than 2 cm - 1.6%
  - > than 2 cm - 18.2%
  - total - 4.6%
- Less radical
  - < than 2 cm - 1.9%

# NACT and Fertility-Sparing Surgery TIP



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



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Gynecologic  
Oncology

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[www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)

## Neoadjuvant chemotherapy and conservative surgery for stage IB1 cervical cancer<sup>☆</sup>

Andrea Maneo <sup>\*</sup>, Stefania Chiari, Cristina Bonazzi, Costantino Mangioni

*Department of Gynecologic Oncology, S. Gerardo Hospital, University of Milan Bicocca, Via Solferino 16, 20052 Monza, Italy*

Received 19 February 2008

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TIP: paclitaxel, ifosfamide, cisplatin

# NACT and Fertility-Sparing Surgery

## TIP

Pathologic characteristics of the patients scheduled for conservative therapy

Patient #	Tumor size (mm)	Histology	Grade	LVSI status	Final procedure	Amount residual	Lymphnode status	Follow-up
1	30	Adenocarcinoma	1	No	Hysterectomy	In situ	Negative	NED
2	10	Squamous	2	No	Hysterectomy	Massive	1 Positive	NED
3	10	Adenocarcinoma	3	No	Hysterectomy	Massive	Negative	NED
4	20	Adenocarcinoma	3	Yes	Hysterectomy	Massive	Negative	NED
5	15	Squamous	3	No	Hysterectomy	Microinvasive	1 Positive	NED
6	10	Squamous	2	No	Conization	Microinvasive	Negative	NED
7	10	Adenosquamous	3	No	Conization	Microinvasive	Negative	NED
8	10	Adenosquamous	1	No	Conization	Negative	Negative	NED
9	15	Adenocarcinoma	1	No	Conization	In situ	Negative	NED
10	30	Adenocarcinoma	1	No	Conization	Microinvasive	Negative	CIN3
11	10	Adenocarcinoma	3	No	Conization	Microinvasive	Negative	NED
12	20	Adenocarcinoma	2	No	Conization	Negative	Negative	NED
13	20	Adenocarcinoma	2	No	Conization	Microinvasive	Negative	CIN2
14	10	Squamous	1	No	Conization	Negative	Negative	CIN1
15	15	Squamous	3	No	Conization	In situ	Negative	NED
16	20	Squamous	3	No	Conization	Negative	Negative	NED
17	10	Adenocarcinoma	1	No	Conization	Massive	Negative	NED
18	10	Adenocarcinoma	3	No	Conization	Microinvasive	Negative	NED
19	15	Squamous	3	No	Conization	Microinvasive	Negative	NED
20	20	Squamous	3	No	Conization	Microinvasive	Negative	NED
21	20	Squamous	1	No	Conization	Negative	Negative	NED

PROM, premature rupture of membranes

# NACT and Fertility-Sparing Surgery

## TIP

Pathologic characteristics of the patients scheduled for conservative therapy

Patient #	Tumor size (mm)	Histology	Grade	LVSI status	Final procedure	Amount residual	Lymphnode status	Follow-up
1	30	Adenocarcinoma	1	No	Hysterectomy	In situ	Negative	NED
2	1							ED
3	1							ED
4	2							ED
5	1							ED
6	1							ED
7	1							ED
8	1							ED
9	1							ED
10	3							N3
11	1							ED
12	2							ED
13	2							IN2
14	1							IN1
15	1							ED
16	2							ED
17	1							ED
18	1							ED
19	1							ED
20	20	Squamous	3	No	Conization	Microinvasive	Negative	NED
21	20	Squamous	1	No	Conization	Negative	Negative	NED

- 9 attempted to become pregnant
- 6 patients became pregnant: 10 pregnancies
  - 1 first-trimester miscarriage
  - 1 PROM <30 weeks
  - 8 term deliveries

PROM, premature rupture of membranes

# NACT and Fertility-Sparing Surgery

## High dose-density cisplatin/ifosfamide or adriamycin

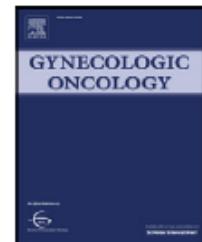
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journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)



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



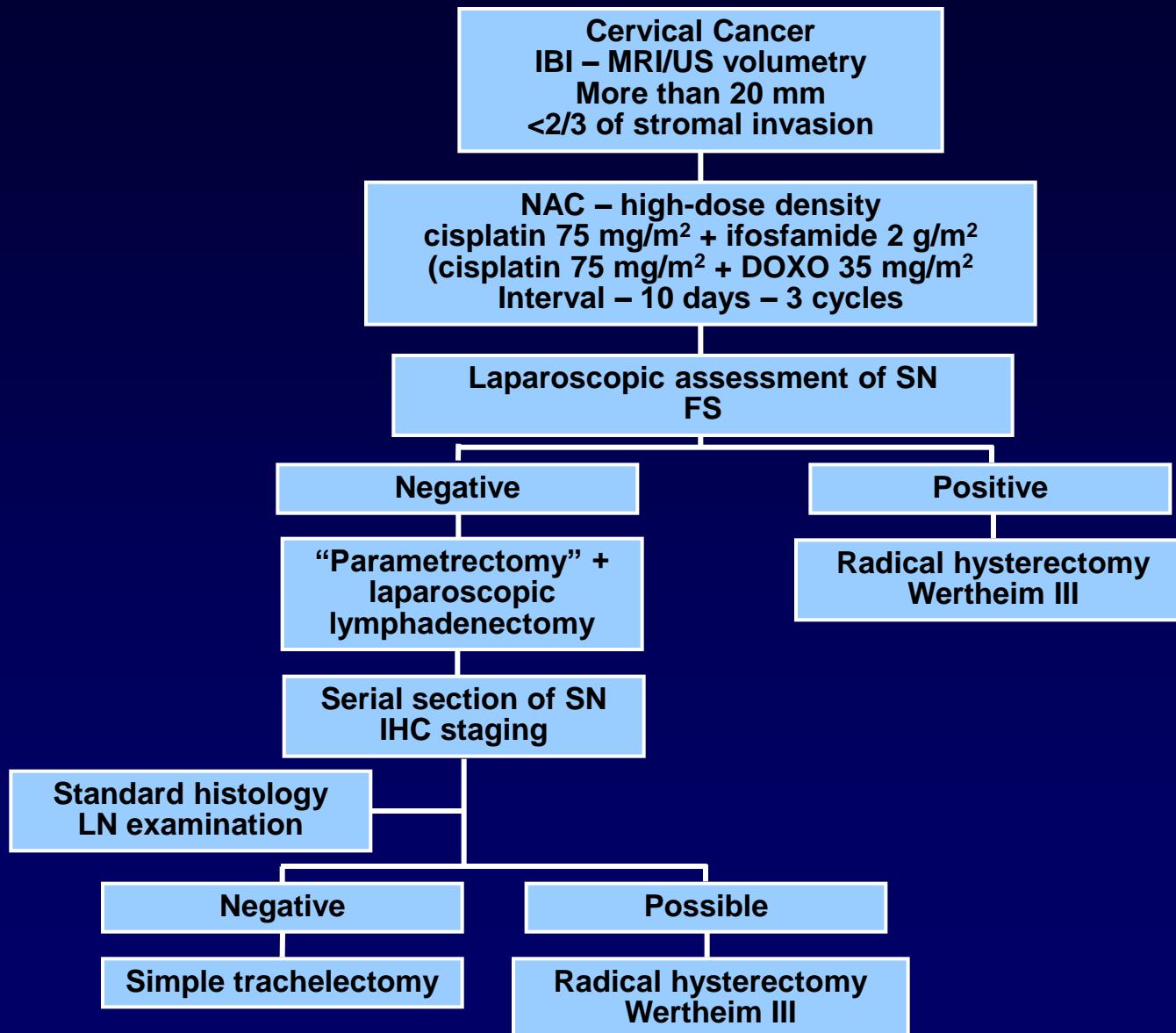
Helena Robova <sup>a</sup>, Michael J. Halaska <sup>a</sup>, Marek Pluta <sup>a</sup>, Petr Skapa <sup>b</sup>, Jan Matecha <sup>a</sup>, Jiri Lisy <sup>c</sup>, Lukas Rob <sup>a,\*</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, 2nd Medical Faculty Charles University Prague, Czech Republic

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# LAP 3/NAC – SLNM and Conversative Surgery (2005)



# LAP 3 Oncologic Outcome

	N Patients		N Patients
Fertility preservation	22	Recurrences	4/22
Immediate RH for positive SLN	4	• local	3
RH for positive margins or patient's decision	6	• ovary	1
Total	<b>32</b>		

# LAP 3 : Obstetric Outcome

- Pregnant women: 11
- 9 women delivered 11 babies
  - 4 premature deliveries: 24 w, 28 w, 34 w, 36 w
  - 7 term deliveries
- 1 first trimester miscarriage
- 1 patient had 2 miscarriages ( second trimester)

# NACT in Cervical Cancer

**NACT**

**Stage**  
**-IB2**  
**-IIA $>4\text{cm}$**   
**-IIB**

**Stage 1B1**  
**Fertility**  
**Sparing**

**RH**

**Conization**

# Locally Advanced Cervical Cancer

All Treatments Require a Multimodality Approach

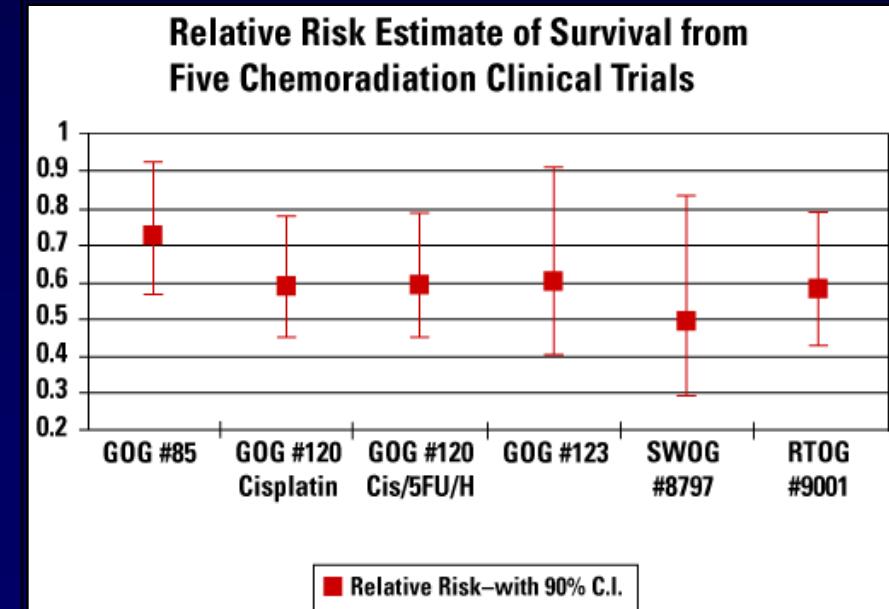
- Chemo/radiation ± chemotherapy
- NACT ⇒ Surgery (or radiotherapy) ± chemo/radiation
- Surgery + chemo/radiation



**Chemoradiation is considered the world standard treatment for LACC**

**Feb-1999: NCI issues clinical announcement on cervical cancer**

*The results of 5 large studies have shown that women with invasive cervical cancer have better survival when they receive chemotherapy that includes the drug cisplatin along with radiation therapy.*



# Locally Advanced Cervical Cancer

Reducing uncertainties about the effects of  
chemoradiotherapy for cervical cancer: individual patient  
data meta-analysis (Review)

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)

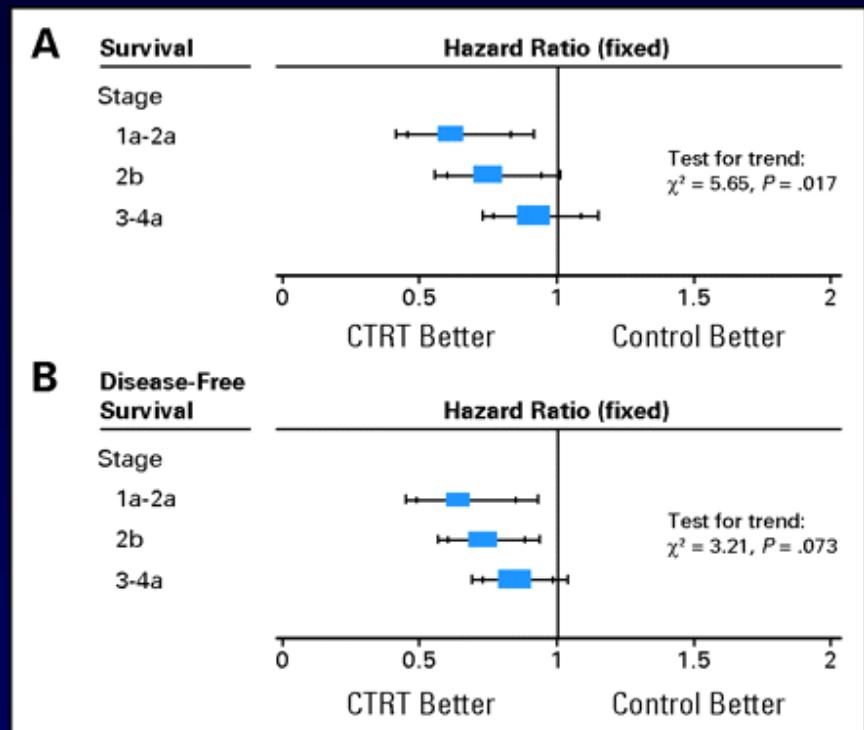


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COLLABORATION®

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration (CCCMAC). *Cochrane Database Syst Rev.*  
2010;(1):CD008285.

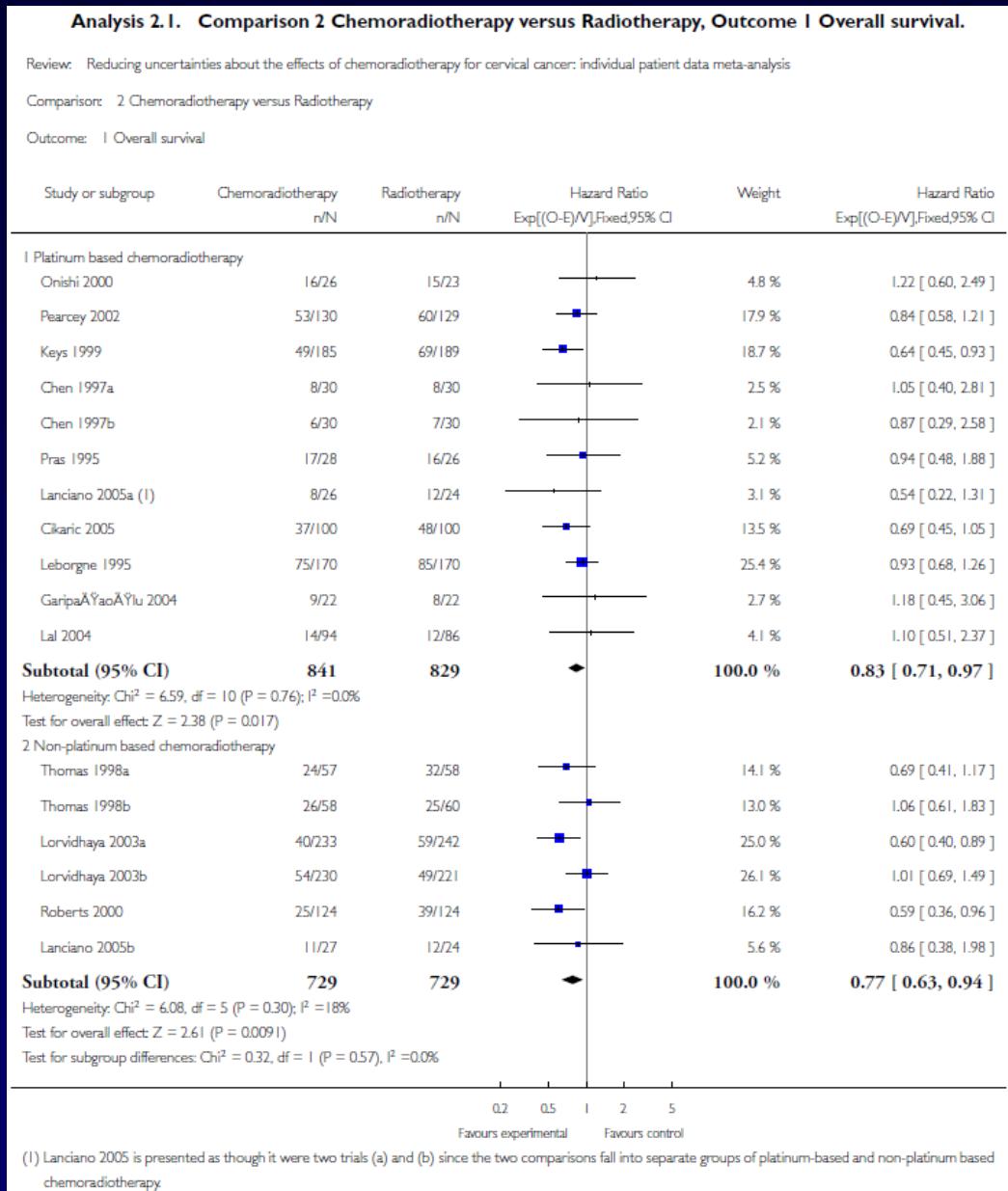
# Locally Advanced Cervical Cancer

- HR correlated with stage
- HR similar for CDDP and non CDDP-based chemo-RT
- HR best for two trials with concurrent and adjuvant CT



# Locally Advanced Cervical Cancer

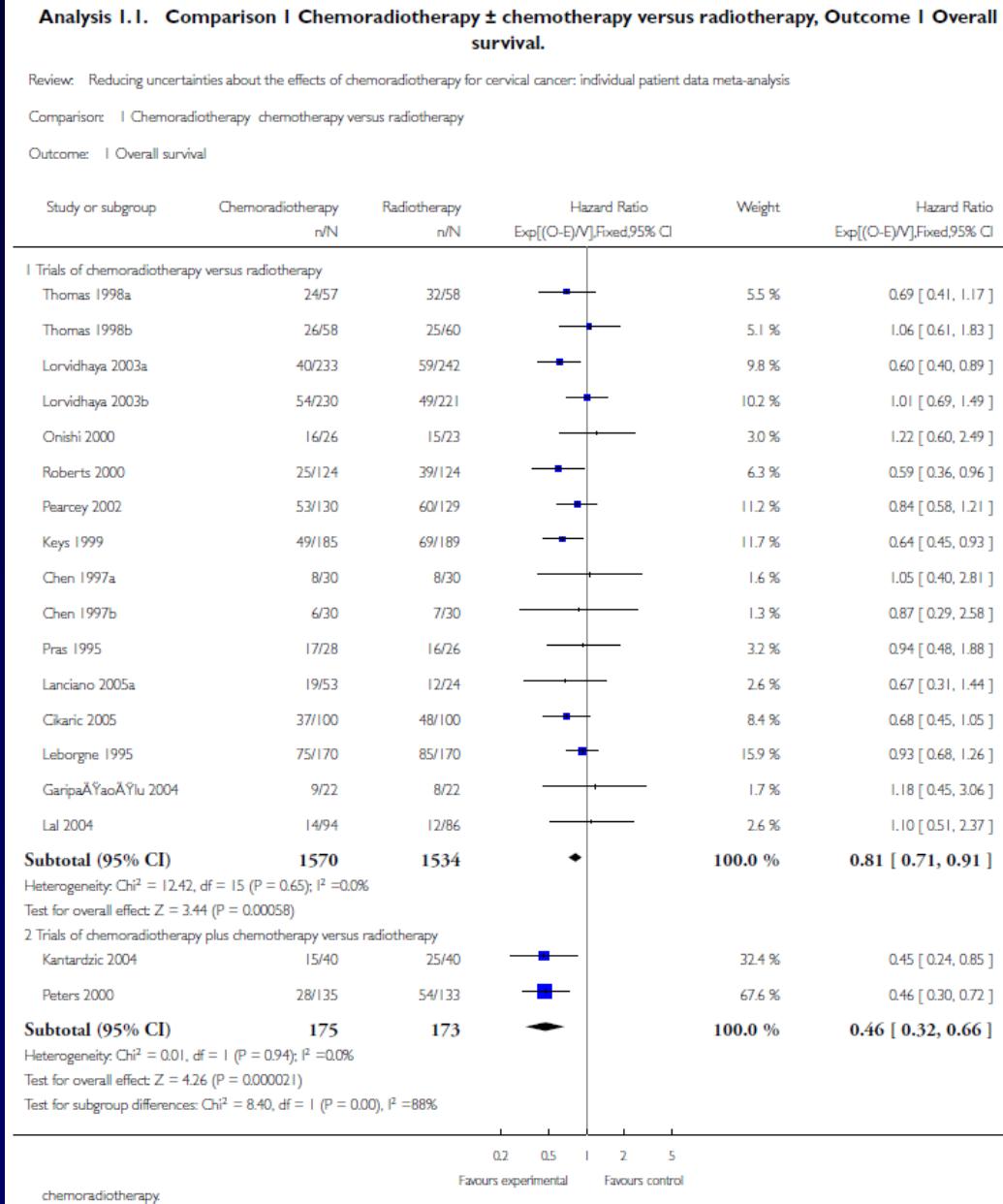
- HR correlated with stage
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- HR best for two trials with concurrent and adjuvant CT



Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis (NACCCMA) Collaboration Collaboration. *Cochrane Database Syst Rev*. 2004;(2):CD001774.

# Locally Advanced Cervical Cancer

- HR correlated with stage
- HR similar for CDDP and non CDDP-based chemo-RT
- HR best for two trials with concurrent and adjuvant CT



Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis (NACCCMA) Collaboration Collaboration. Cochrane Database Syst Rev. 2004;(2):CD001774.

# Why Should We Consider NACT ?

- Reduction of tumor burden
- Decrease of distal metastases and eradication of micrometastases
- Allows surgery in countries with fewer available radiotherapy centers
- Better long-term QoL compared with Ch/RT in young patients

# Locally Advanced Cervical Cancer

**Neoadjuvant chemotherapy for locally advanced cervix  
cancer (Review)**

Tierney J, Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration  
(NACCCMA) Collaboration



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COLLABORATION®**

Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration (NACCCMA) Collaboration. *Cochrane Database Syst Rev.* 2004;(2):CD001774.

**Is NACT followed by RT better  
than RT alone?**

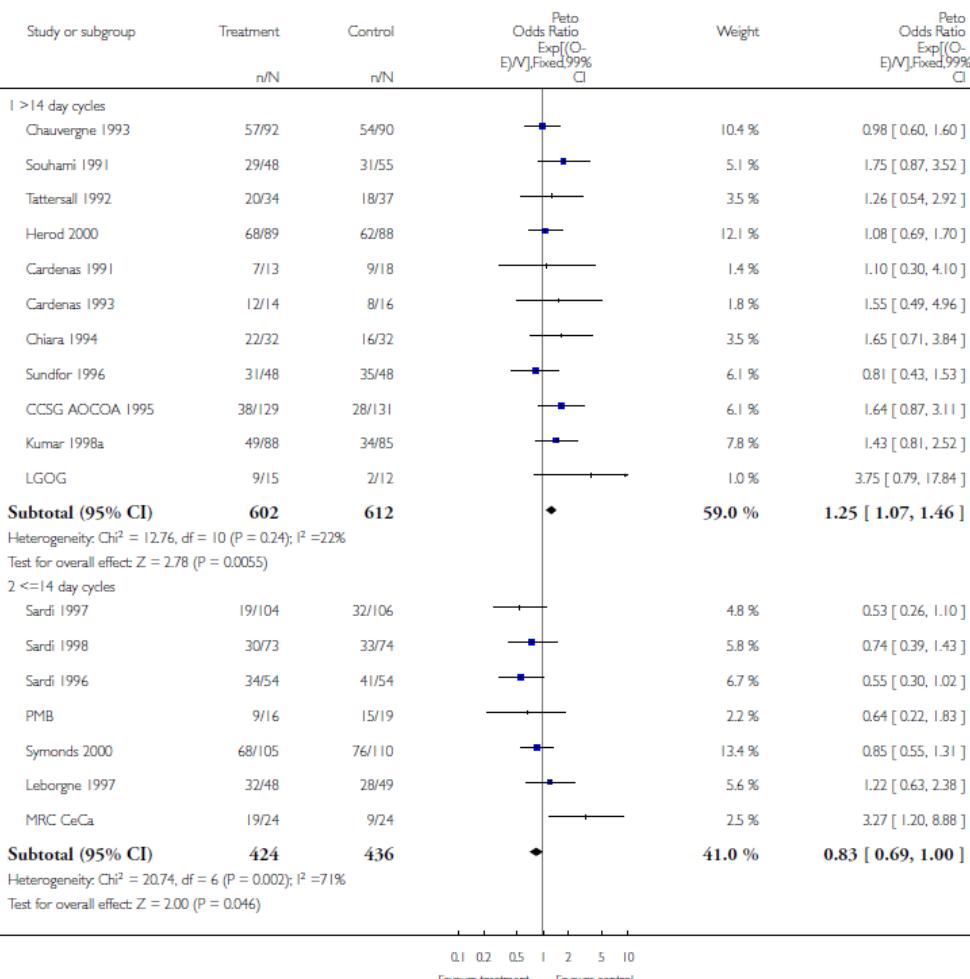
# Locally Advanced Cervical Cancer NACT & RT vs RT

## Analysis I.1. Comparison I Treatment comparison I, Outcome I Survival by planned neoadjuvant cycle length.

Review: Neoadjuvant chemotherapy for locally advanced cervix cancer

Comparison: I Treatment comparison I

Outcome: I Survival by planned neoadjuvant cycle length



| > | 4 day cycles



1.25 [ 1.07, 1.46 ]

2 <= | 4 day cycles



0.83 [ 0.69, 1.00 ]

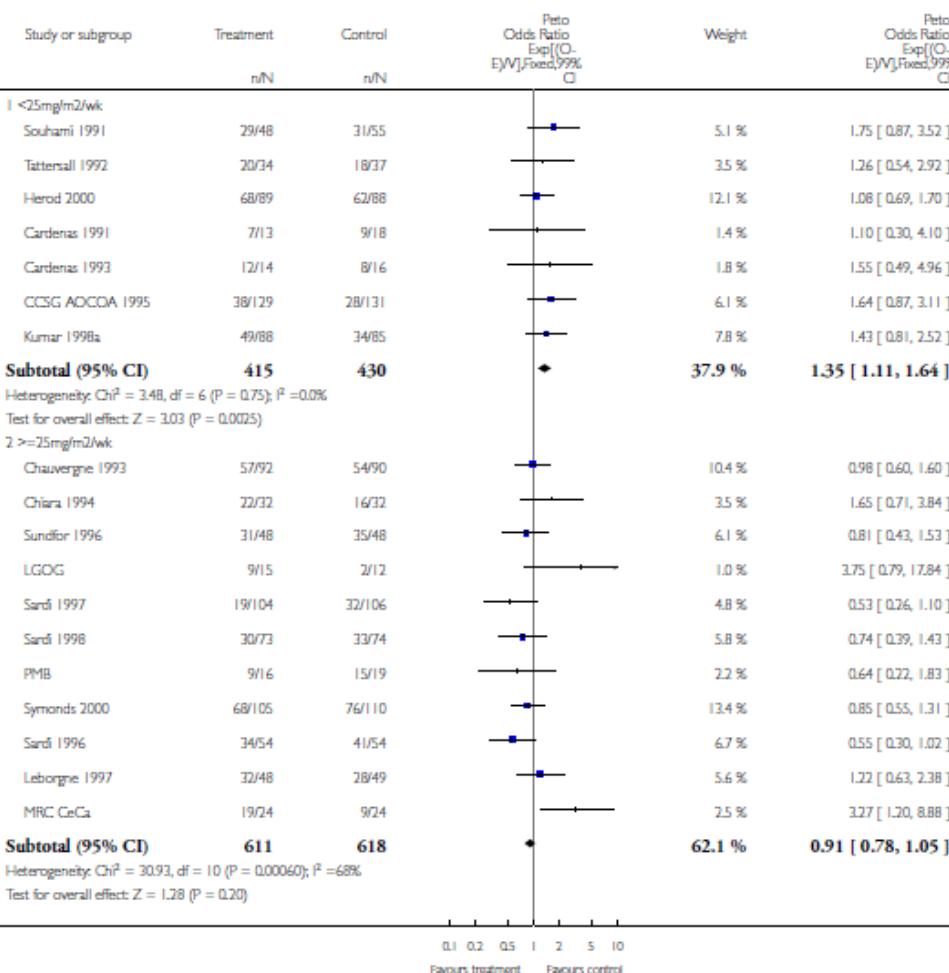
# Locally Advanced Cervical Cancer NACT & RT vs RT

**Analysis 1.3. Comparison I Treatment comparison I, Outcome 3 Survival by planned cisplatin dose intensity.**

Review: Neoadjuvant chemotherapy for locally advanced cervix cancer

Comparison: I Treatment comparison I

Outcome: 3 Survival by planned cisplatin dose intensity



| <25mg/m<sup>2</sup>/wk



1.35 [ 1.11, 1.64 ]

2 ≥=25mg/m<sup>2</sup>/wk



0.91 [ 0.78, 1.05 ]

**Is NACT followed by radical  
surgery better than RT alone?**

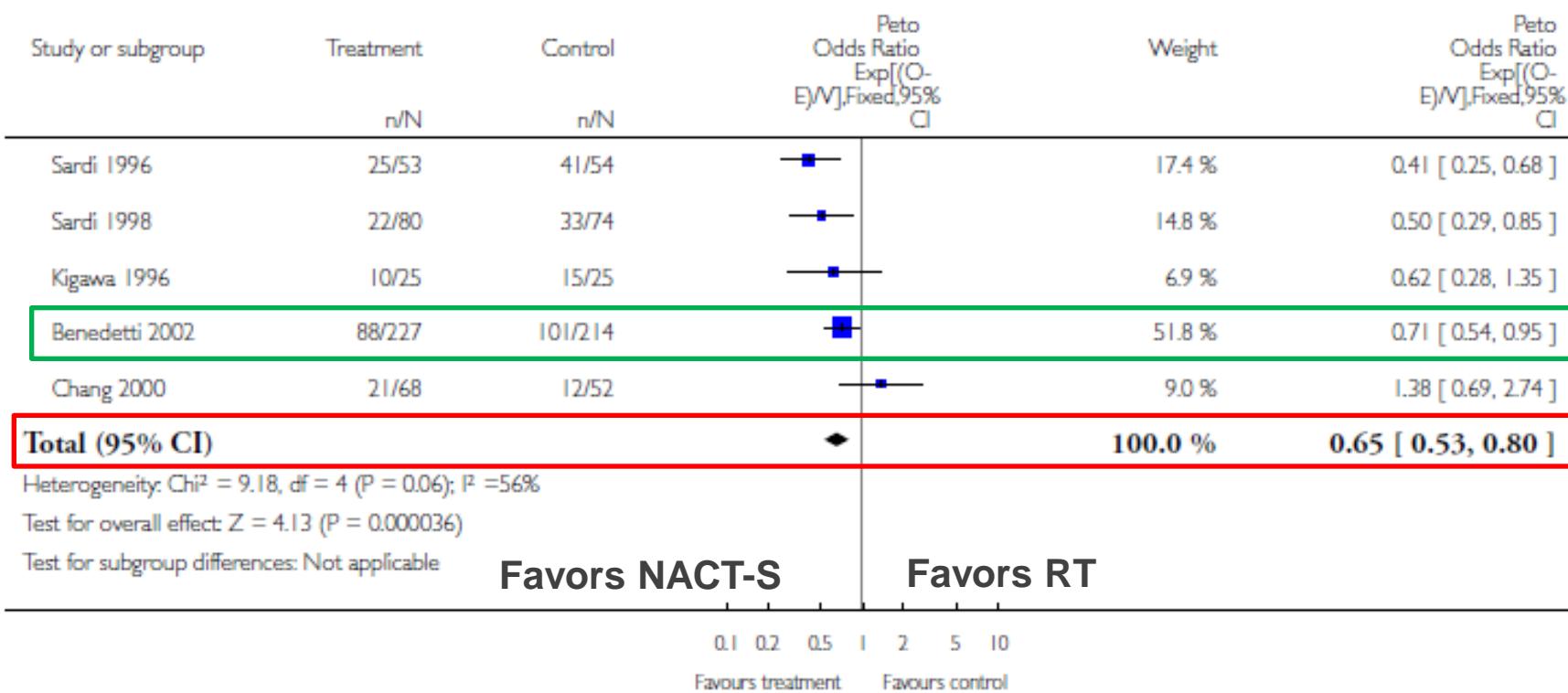
# Locally Advanced Cervical Cancer NACT & S vs RT

## Analysis 2.1. Comparison 2 Treatment comparison 2, Outcome I Survival.

Review: Neoadjuvant chemotherapy for locally advanced cervix cancer

Comparison: 2 Treatment comparison 2

Outcome: I Survival



**Is NACT followed by radical  
surgery better than radical  
surgery alone?**

# Locally Advanced Cervical

**Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer (Review)**

Rydzewska L, Tierney J, Vale CL, Symonds PR



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# Locally Advanced Cervical Cancer

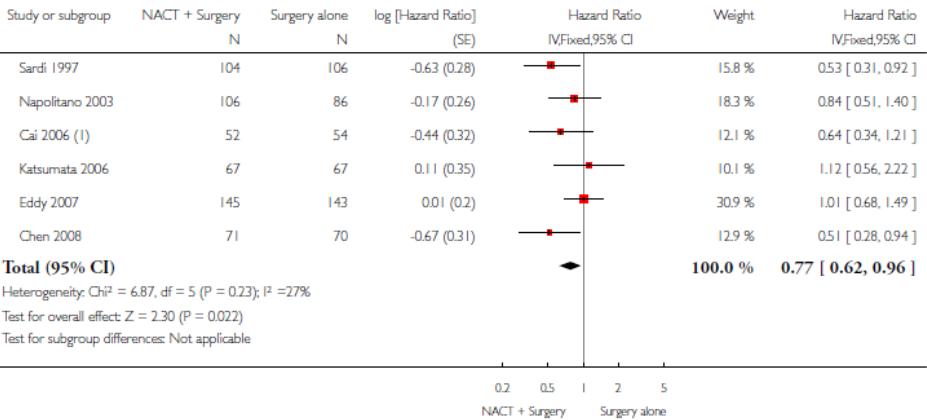
- Better OS and PFS for NACT/RS vs RS
- Fewer local recurrences
- Fewer distant recurrences
- More radical resections
- Less N +
- Less parametrial involvement

## Analysis 1.1. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome I Overall survival (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: I Overall survival (fixed-effect analysis)

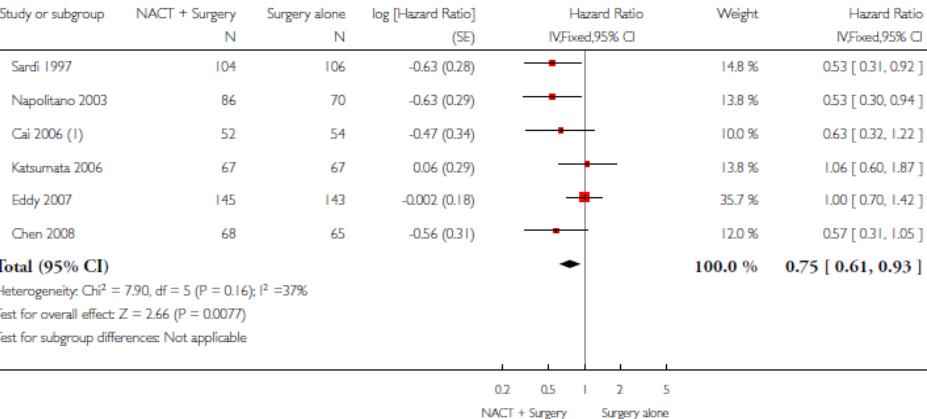


## Analysis 1.3. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 3 Progression-free survival (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 3 Progression-free survival (fixed-effect analysis)



# Locally Advanced Cervical Cancer

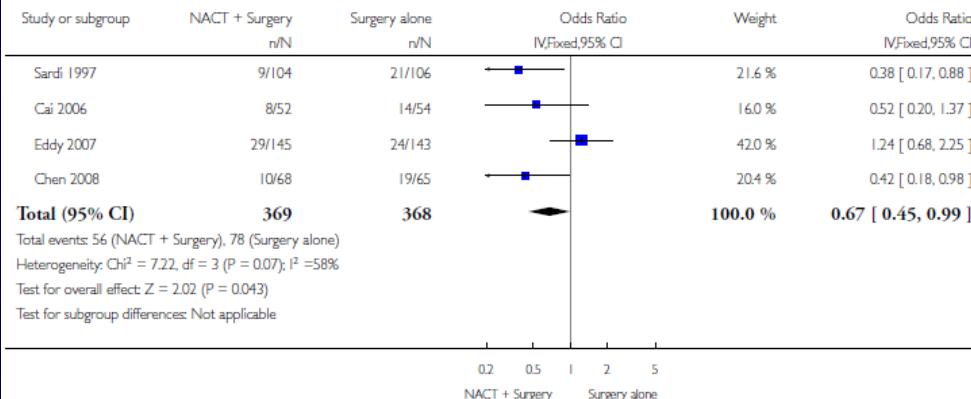
- Better OS and PFS for NACT/RS vs RS
- Fewer local recurrences
- Fewer distant recurrences
- More radical resections
- Less N +
- Less parametrial involvement

**Analysis 1.5. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 5 Rates of local recurrence (fixed-effect analysis).**

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 5 Rates of local recurrence (fixed-effect analysis)

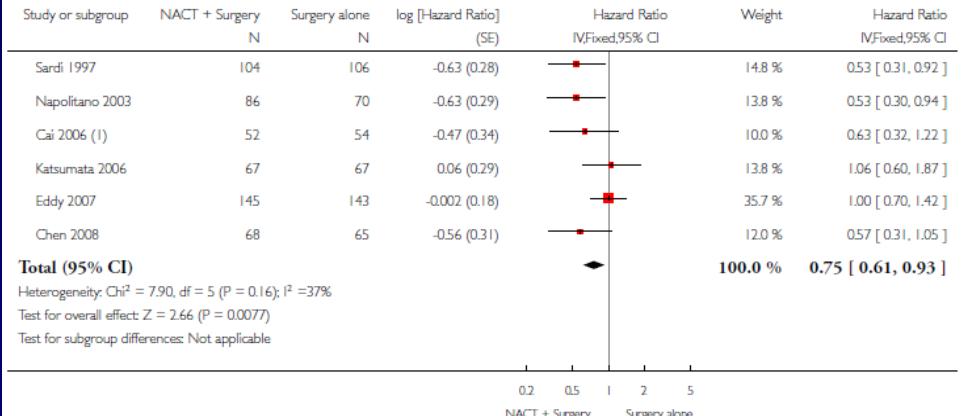


**Analysis 1.3. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 3 Progression-free survival (fixed-effect analysis).**

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 3 Progression-free survival (fixed-effect analysis)



# Locally Advanced Cervical Cancer

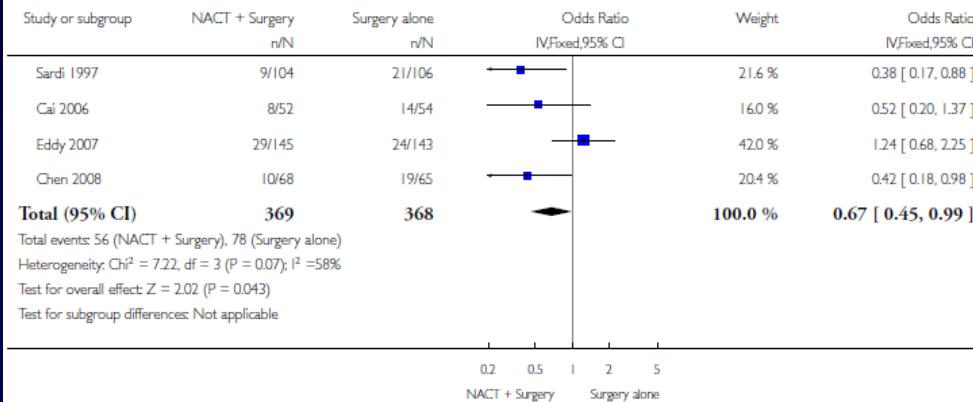
- Better OS and PFS for NACT/RS vs RS
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- Less parametrial involvement

Analysis 1.5. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 5 Rates of local recurrence (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 5 Rates of local recurrence (fixed-effect analysis)

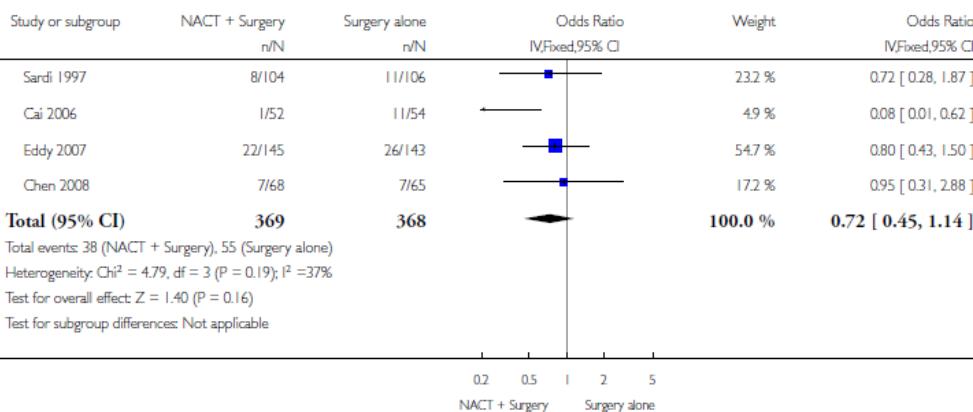


Analysis 1.7. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 7 Rates of distant recurrence (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 7 Rates of distant recurrence (fixed-effect analysis)



# Locally Advanced Cervical Cancer

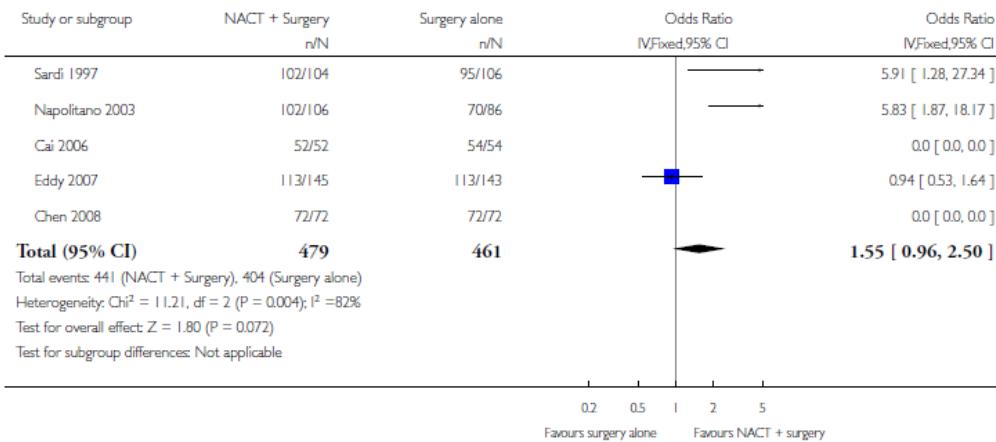
- Better OS and PFS for NACT/RS vs RS
- Fewer local recurrences
- Fewer distant recurrences
- More radical resections
- Less N +
- Less parametrial involvement

Analysis 1.9. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 9 Rates of radical resection (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 9 Rates of radical resection (fixed-effect analysis)

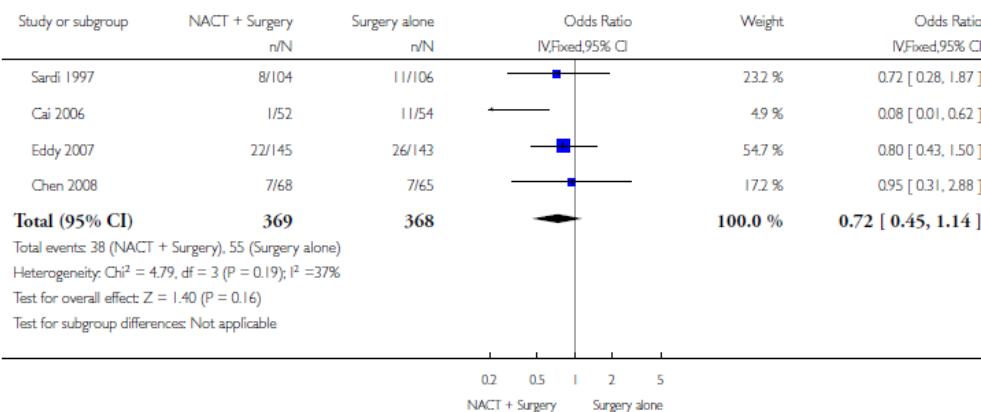


Rates of distant recurrence (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 7 Rates of distant recurrence (fixed-effect analysis)



# Locally Advanced Cervical Cancer

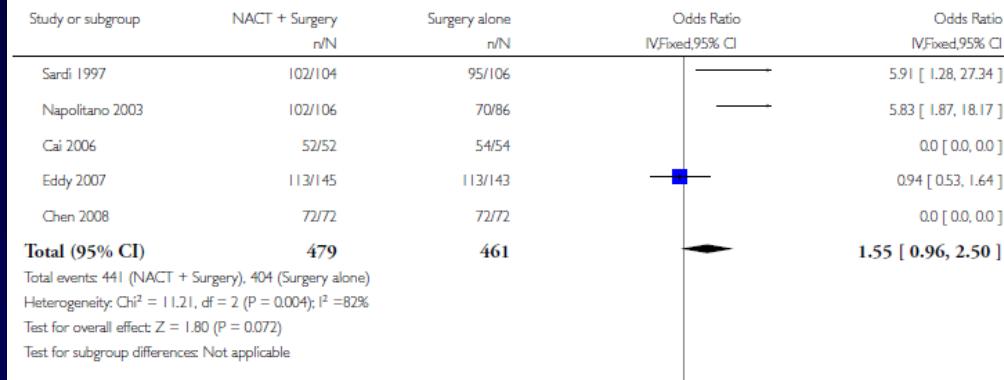
- Better OS and PFS for NACT/RS vs RS
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- Less parametrial involvement

## Analysis 1.9. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 9 Rates of radical resection (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 9 Rates of radical resection (fixed-effect analysis)

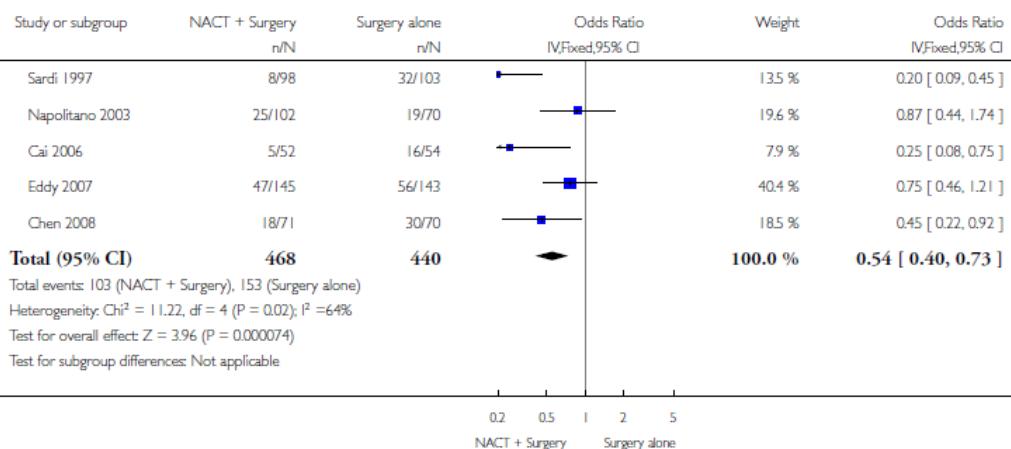


## Analysis 1.11. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 11 Rates of pathological findings - lymph node metastases or positive lymph nodes (fixed-effect analysis).

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 11 Rates of pathological findings - lymph node metastases or positive lymph nodes (fixed-effect analysis)



# Locally Advanced Cervical Cancer

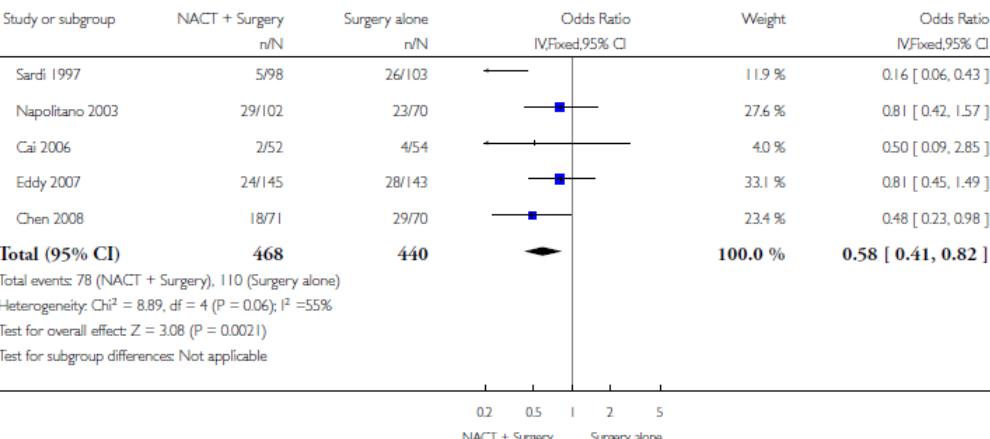
- Better OS and PFS for NACT/RS vs RS
- Fewer local recurrences
- Fewer distant recurrences
- More radical resections
- Less N +
- Less parametrial involvement

**Analysis 1.13. Comparison I Neoadjuvant chemotherapy plus surgery versus surgery alone, Outcome 13 Rates of pathological findings - parametrial infiltration (fixed-effect analysis).**

Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

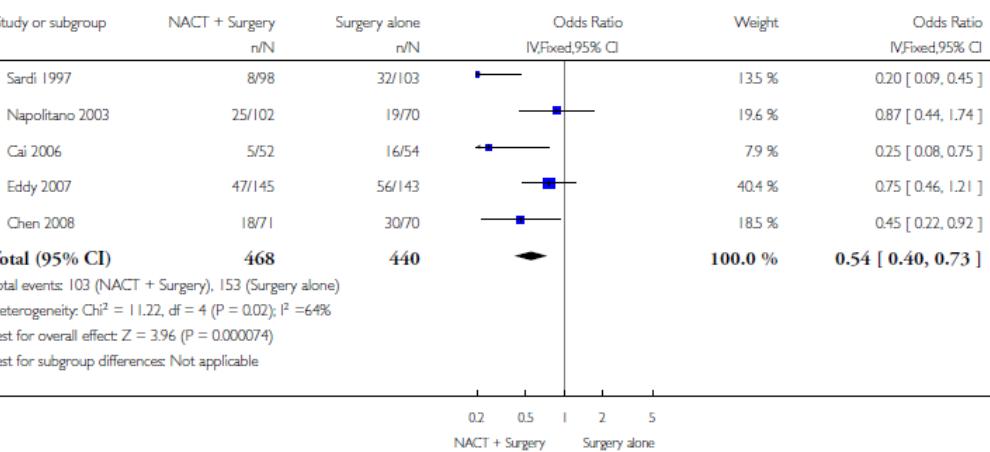
Outcome: 13 Rates of pathological findings - parametrial infiltration (fixed-effect analysis)



Review: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Comparison: I Neoadjuvant chemotherapy plus surgery versus surgery alone

Outcome: 11 Rates of pathological findings - lymph node metastases or positive lymph nodes (fixed-effect analysis)



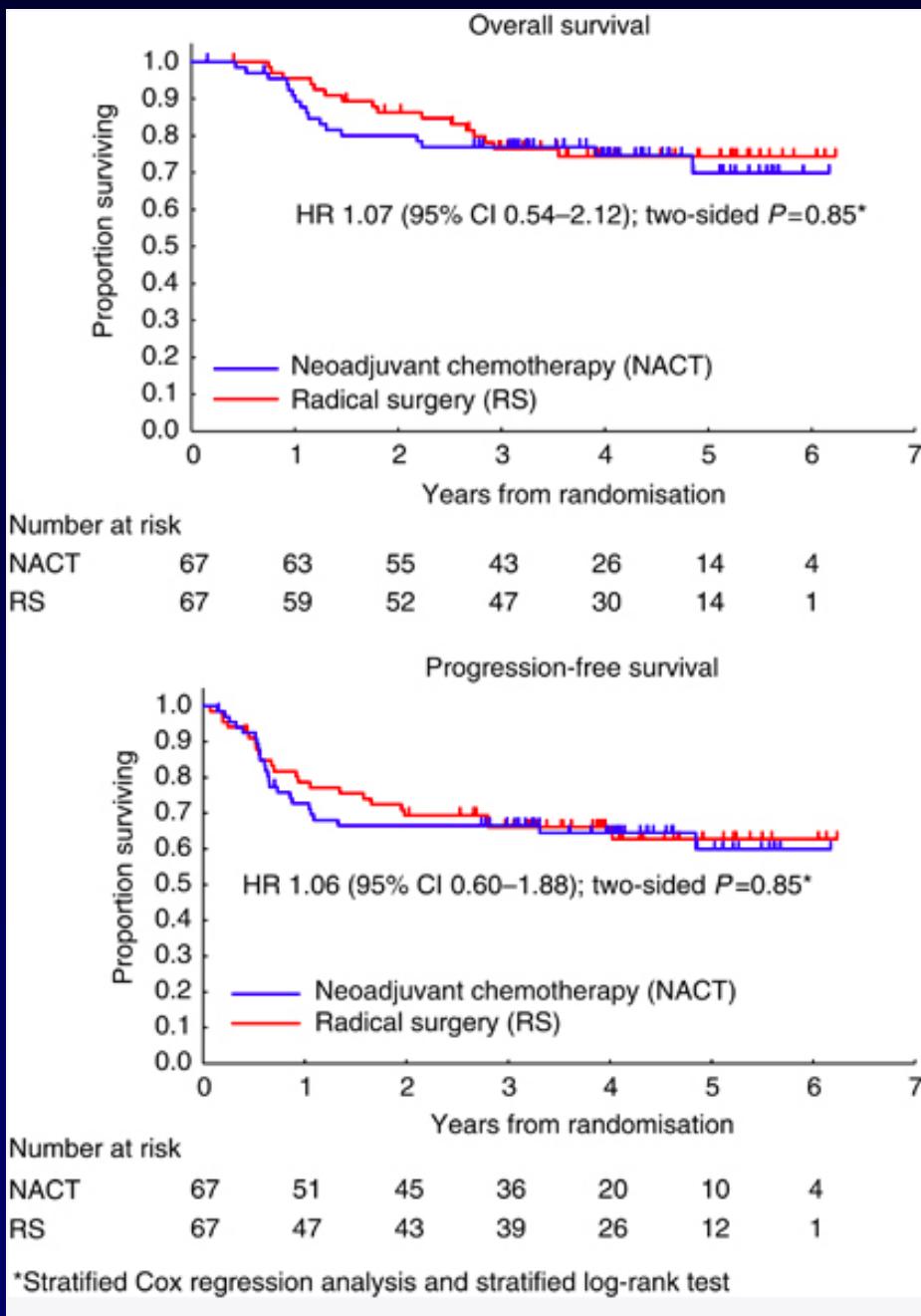
Keywords: cervical cancer; neoadjuvant chemotherapy; phase III trial; radical surgery

# Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery vs radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: a Japan Clinical Oncology Group trial (JCOG 0102)

N Katsumata<sup>\*1</sup>, H Yoshikawa<sup>2</sup>, H Kobayashi<sup>3</sup>, T Saito<sup>4</sup>, K Kuzuya<sup>5</sup>, T Nakanishi<sup>6</sup>, T Yasugi<sup>7</sup>, N Yaegashi<sup>8</sup>, H Yokota<sup>9</sup>, S Kodama<sup>10</sup>, T Mizunoe<sup>11</sup>, M Hiura<sup>12</sup>, T Kasamatsu<sup>13</sup>, T Shibata<sup>14</sup> and T Kamura<sup>15</sup> on behalf of the Japan Clinical Oncology Group

<sup>1</sup>Department of Medical Oncology, Nippon Medical School Musashikosugi Hospital, Kawasaki, Japan; <sup>2</sup>Department of Obstetrics and Gynecology, University of Tsukuba, Tsukuba, Japan; <sup>3</sup>Department of Obstetrics and Gynecology, Kyushu University, Fukuoka, Japan; <sup>4</sup>Department of Gynecologic Oncology, Kyushu Cancer Center, Fukuoka, Japan; <sup>5</sup>Kuzuya Clinic, Nagoya, Japan;

<sup>6</sup>Department of Gynecologic Oncology, Aichi Cancer Center, Nagoya, Japan; <sup>7</sup>Department of Obstetrics and Gynecology, Tokyo University, Tokyo, Japan; <sup>8</sup>Department of Obstetrics and Gynecology, Tohoku University, Sendai, Japan; <sup>9</sup>Department of Gynecologic Oncology, Saitama Cancer Center, Saitama, Japan; <sup>10</sup>Department of Gynecologic Oncology, Niigata Cancer Center, Niigata, Japan; <sup>11</sup>Department of Gynecologic Oncology, Kure Medical Center, Kure, Japan; <sup>12</sup>Department of Gynecologic Oncology, Shikoku Cancer Center, Matsuyama, Japan; <sup>13</sup>Department of Gynecologic Oncology, National Cancer Center Hospital, Tokyo, Japan; <sup>14</sup>Japan Clinical Oncology Group Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo, Japan and <sup>15</sup>Department of Obstetrics and Gynecology, Kurume University, Kurume, Japan



# **What Have We Learned So Far? Take-Home Messages**

- 1. Chemoradiation is better than radiation alone in the treatment of LACC**
- 2. NACT followed by RT might be detrimental or beneficial according to platinum dose and schedule**
- 3. NACT-radical surgery is better than radiation alone in the treatment of LACC**
- 4. NACT-radical surgery is better than surgery alone in the treatment of LACC**
- 5. No data yet on NACT-radical surgery versus chemoradiation**

# **What Have We Learned So Far? Take-Home Messages**

- 1. Chemoradiation is better than radiation alone in the treatment of LACC**
- Chemotherapy is needed in the treatment of locally advanced cervical cancer**
- 4. NACT-radical surgery is better than surgery alone in the treatment of LACC**
- 5. No data yet on NACT-radical surgery versus chemoradiation**

# EORTC - #55994

## RCT Comparing NACT+RS Versus CT/RT

Cervical Cancer  
IB2, IIA $>4$ cm, IIB

RANDOMIZED

NACT +  
SURGERY

Exclusive  
Chemoradiation



# Which kind of chemotherapy ?

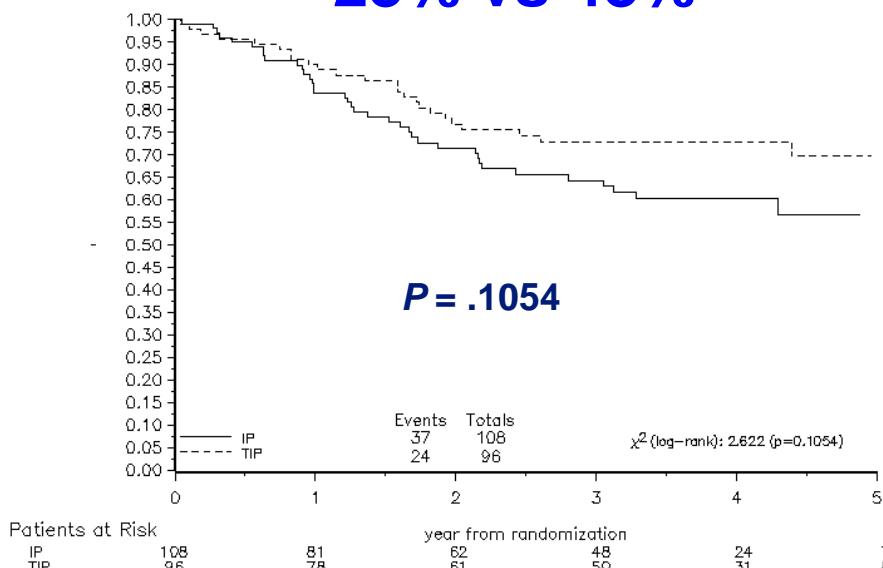
# **Every (almost) Regimen Is Possible**

- Cisplatin or carboplatin (or nedaplatin)
- Combination with
  - Vincristine
  - Bleomycin
  - Paclitaxel/docetaxel
  - 5-FU
  - Ifosfamide
  - Gemcitabine
- Administered intravenously or with intra-arterial infusion + embolization

# Overall Survival

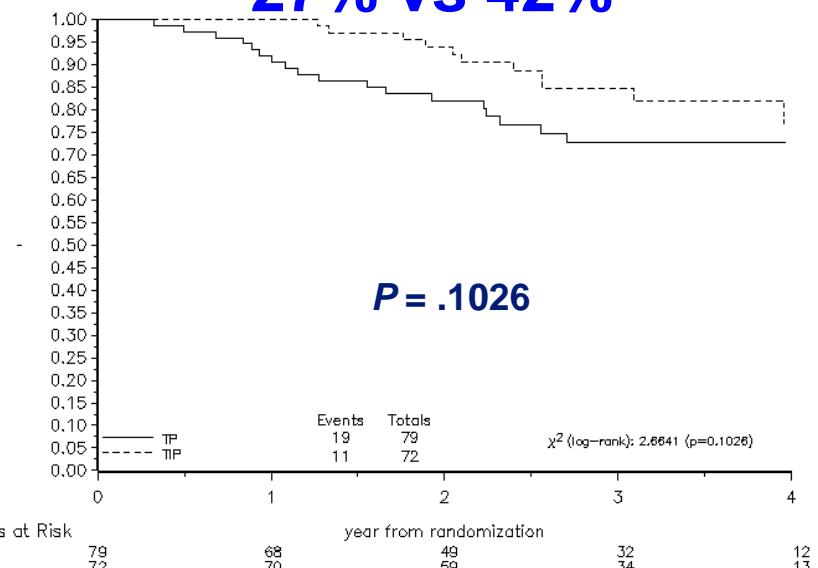
SNAP 01: IP vs TIP

'sopravvivenza e trattamento'  
**Optimal response:**  
**23% vs 48%**



SNAP 02: TP vs TIP

'sopravvivenza e trattamento'  
**Optimal response:**  
**27% vs 42%**



Buda A, et al. *J Clin Oncol.* 2005;23(18):4137-4145.

Lissoni AA, et al. *Ann Oncol.* 2009;20(4):660-665.

Keywords: neoadjuvant chemotherapy; locally advanced; cervical cancer

## A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer

M McCormack<sup>\*1</sup>, L Kadalayil<sup>2</sup>, A Hackshaw<sup>2</sup>, M A Hall-Craggs<sup>1</sup>, R P Symonds<sup>3</sup>, V Warwick<sup>2</sup>, H Simonds<sup>1</sup>, I Fernando<sup>4</sup>, M Hammond<sup>2</sup>, L James<sup>2</sup>, A Feeney<sup>2</sup> and J A Ledermann<sup>2</sup>

<sup>1</sup>University College London Hospitals, 250 Euston Road, London NW1 2PG, UK; <sup>2</sup>CR-UK and UCL Cancer Trials Centre, University College of London, London, UK; <sup>3</sup>Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK and <sup>4</sup>Queen Elizabeth Hospital, Birmingham, UK

# Carboplatin AUC2 & Paclitaxel 80 mg/m<sup>2</sup>

## Weeks 1-6

### Tumor Response Using RECIST Criteria

	Post-Neoadjuvant - N = 46, 12 Wks After All Treatment - N = 46, N (%)	N (%)
Complete response	2 (4)	29 (63)
Partial response	30 (65)	10 (22)
Stable disease	10 (22)	2 (4)
Progressive disease	2 (4)	2 (4)
Assessment not done	2 (4) <sup>a</sup>	3 (7) <sup>b</sup>

<sup>a</sup>One patient died after cycle 1, and the other had a serious adverse event after starting treatment, so stopped early

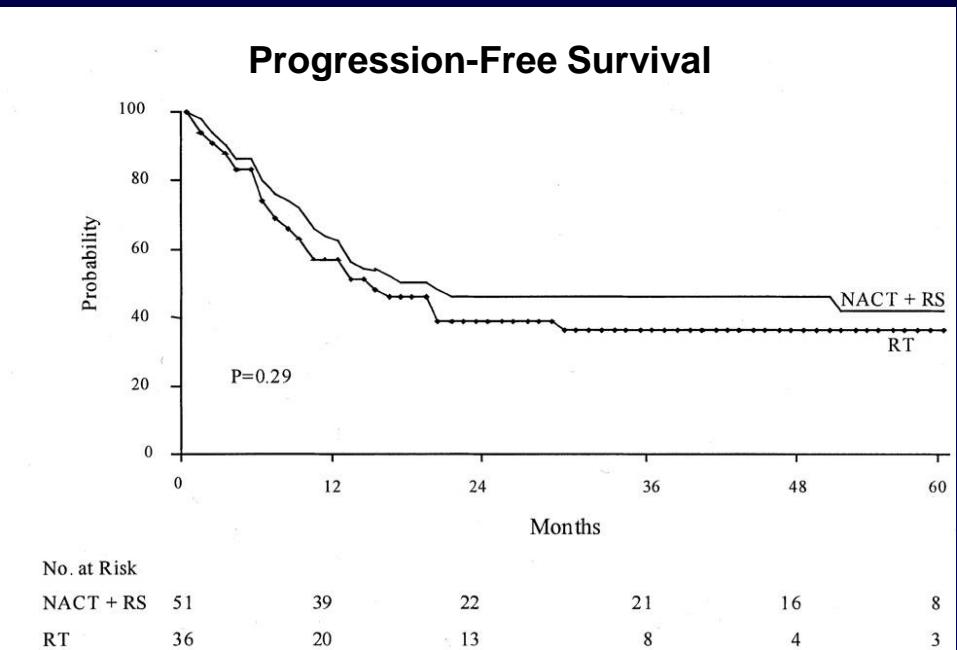
<sup>b</sup>The same two patients as above and a third patient due to progressive disease and clinician's choice

# **NACT/Surgery Relevant Questions**

- Which patients will not benefit ?
- Can we identify them?
- Which patients will benefit the most?
- How can we further improve?

# Which Patients Will Not Benefit?

## Stage III



ARM value	5y S	Pts	P
<b>NACT+S</b>	<b>41</b>	<b>51</b>	
<b>RT</b>	<b>36</b>	<b>36</b>	<b>.36</b>

# Which Patients Will Not Benefit?

- Stage III
- Who else?

# Multivariate Analysis EIO Experience

Variable	Classification	PFS		OS	
		RR (95%CI)	P value	HR (95%CI)	P value
<b>Response to NACT</b>	<b>SD vs CR+pPR1+pPR2</b>	<b>2.0 (1.1-3.6)</b>	<b>0.017</b>	<b>2.7 (1.3-5.7)</b>	<b>.007</b>
<b>Lymph node involvement</b>	<b>positive vs negative</b>	<b>1.6 (0.9-2.9)</b>	<b>0.094</b>	<b>2.6 (1.2-5.3)</b>	<b>.001</b>
<b>Parametrial involvement</b>	<b>positive vs negative</b>	<b>2.0 (0.9-4.8)</b>	<b>0.103</b>	<b>2.6 (1.0-6.6)</b>	<b>.052</b>

# **Reasons For Not Giving NACT if Node-Positive**

- **Is chemotherapy less effective on lymph nodes?**
- **If nodes positive at time of surgery, radiation needed anyhow; therefore patients will receive three treatment modalities with associated increased morbidity**

# Is chemotherapy less effective on nodes? NACT + Surgery vs Primary Surgery

## Pathologic Findings From Surgical Specimen

Groups	Lymph Node Metastasis Rate	P Value	Parametrial Infiltration Rate	P Value
<b>Therapy modality</b>				
NACT group	25.0% (18/72)	.025	25.0% (18/72)	.038
Primary surgery group	42.9% (30/70)		41.4% (29/70)	
<b>Response to NACT</b>				
Responders	16.0% (8/50)	.008	16.0% (8/50)	.008
Nonresponders	45.5% (10/22)		45.5% (10/22)	

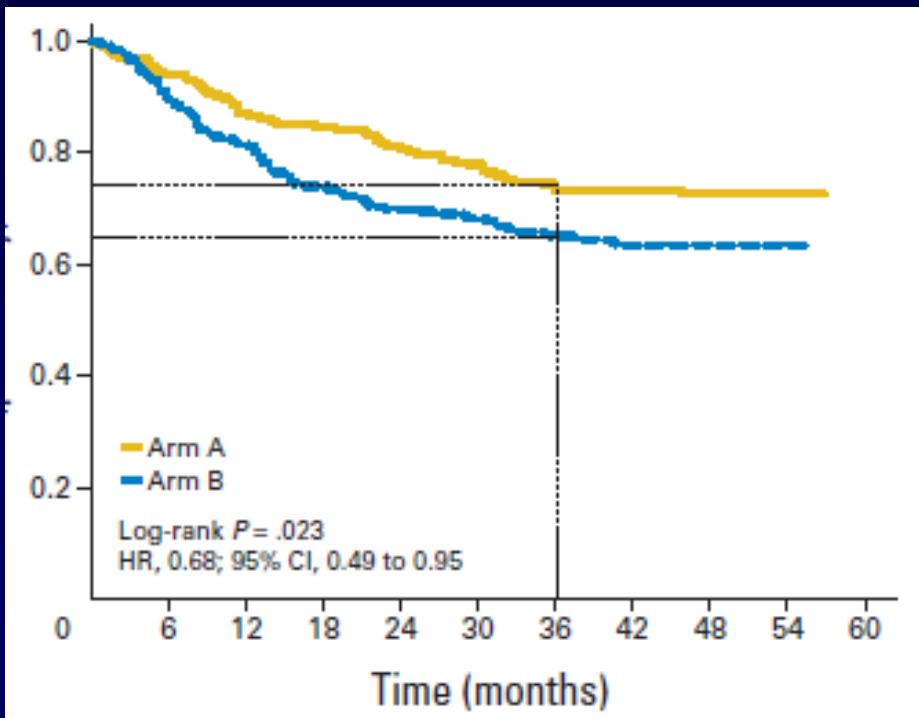
No significant difference in complication morbidity was detected between the NACT group and the primary surgery group (22.2%, 16/72 in NACT group; 25.7%, 18/70 in primary surgery group,  $P = .626$ ).

# Who Will Not Benefit ?

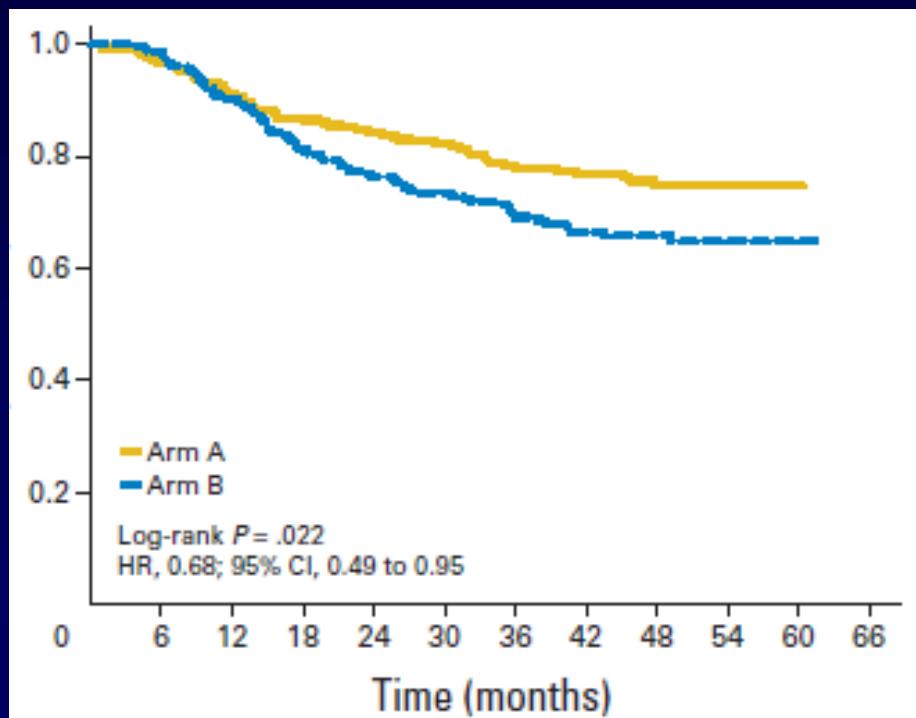
- Should we exclude from NACT/surgery all patients with positive nodes at primary diagnosis?
  - Probably not
- Should we exclude from surgery only those with persistent positive nodes after NACT?
  - Probably yes
- Can their prognosis be improved?
  - Extended-field irradiation ?
- Can their morbidity be decreased by sparing one modality?
  - Yes
- If yes, which modality shoud be spared?
  - Chemotherapy?
  - Surgery on the primary tumor?

# Chemo-RT for LACC Concomitant and Adjuvant

## Progression-Free Survival



## Overall Survival





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# THE OUTBACK TRIAL

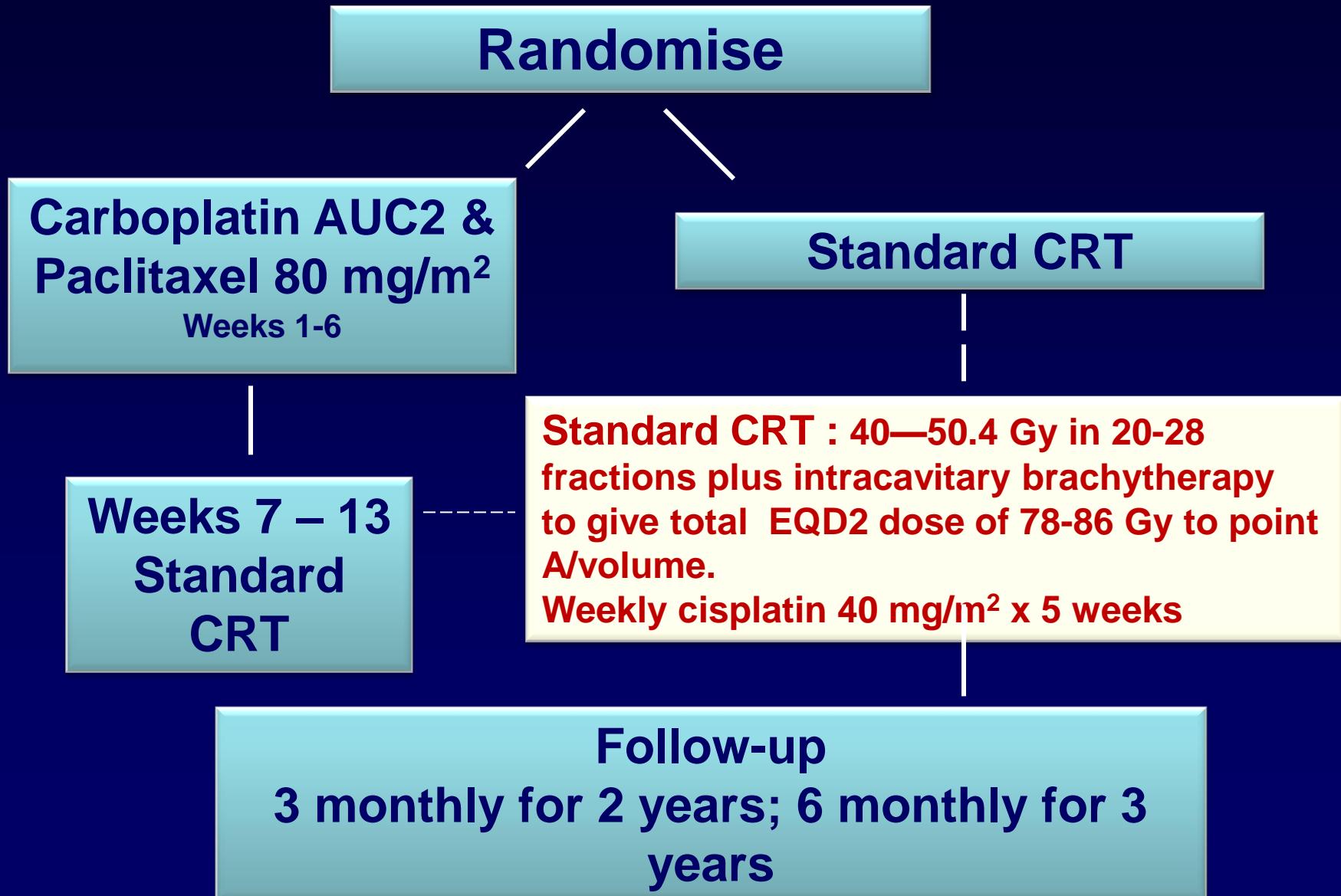
A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone

ANZGOG



The University of Sydney

# INTERLACE Trial



# **Systemic Chemotherapy May Be Needed Anyhow in the Treatment of LACC**

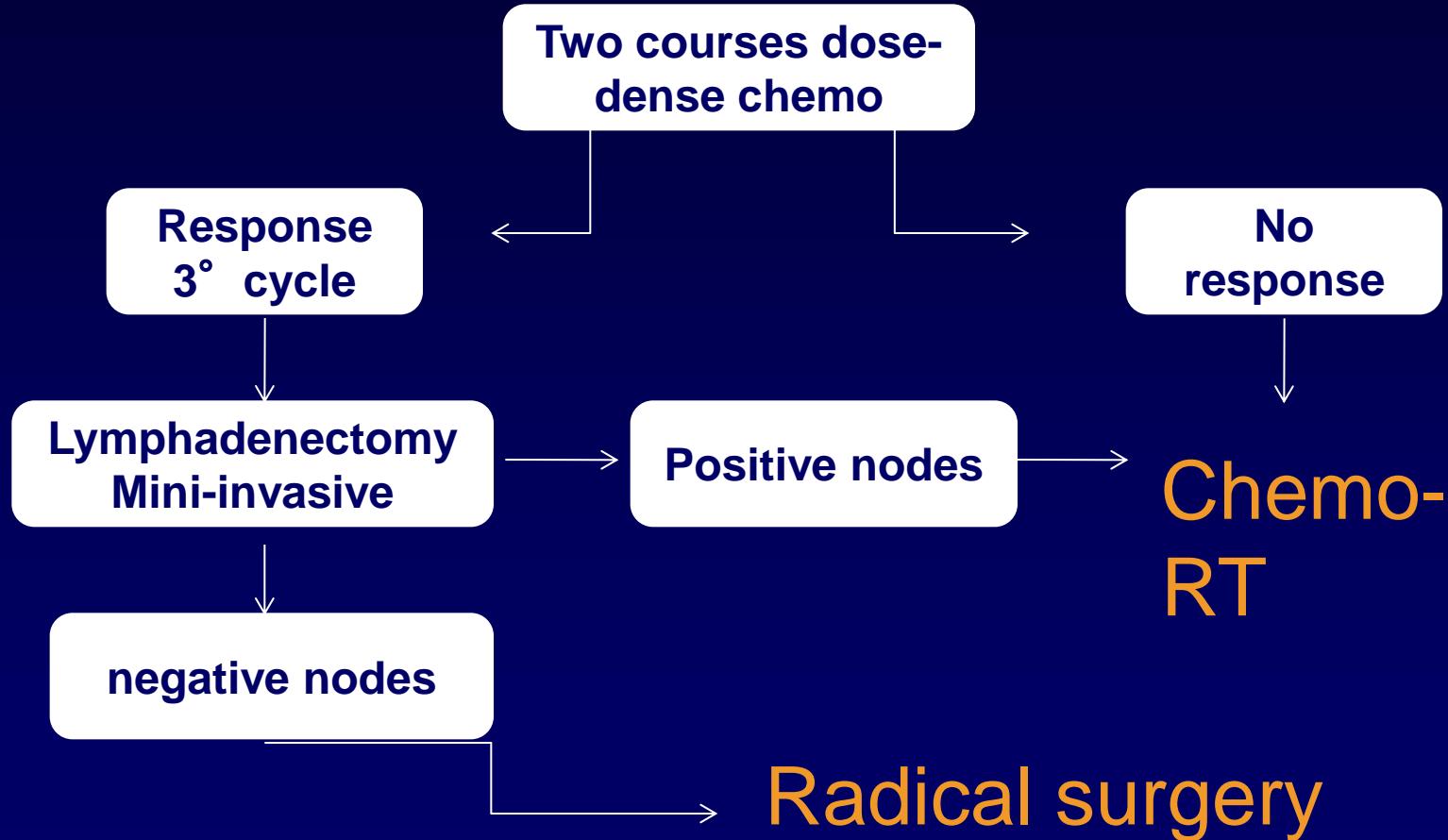
- As adjuvant to chemo-RT
- As neoadjuvant to surgery
- We should avoid the concomitant use of surgery and radiotherapy
- We will not be able to avoid the concomitant use of chemo and surgery or chemo and radiation

# **Which Patients Will Not Benefit After NACT..... from surgery ?**

- **Patients with persistent positive nodes after chemo**
- **Who can best be identified through lymphadenectomy**
- **Who may benefit from extended-field irradiation**
- **Who may be spared from the increased morbidity of surgery and radiotherapy**

# The Future: How to Improve?

If chemo is needed anyhow even with chemo-RT



# The Future: How to Improve?

If chemo is needed anyhow even with chemo-RT

Two courses dose-

Pts will receive the best treatment in case of positive nodes: extended-field chemo-RT + chemo

And in case of negative node:  
NACT/surgery

Radical surgery

# Conclusions

- NACT followed by surgery is more effective than either surgery or radiotherapy alone
- Still waiting for the results of EORTC 55994 to confirm the superiority of NACT + surgery vs chemo-RT
- An ongoing trial (Interlace) will assess the role of NACT + chemo-RT vs chemo-RT
- Chemotherapy is becoming increasingly important in the treatment of locally advanced cervical cancer:
  - As adjuvant /neoadjuvant to chemo-RT
  - As neoadjuvant to surgery
- Key to success will be patient selection in order to identify which patients will benefit the most from each modality

# 2015

## Progress and Controversies in Gynecologic Oncology Conference

