

# **Role of Neoadjuvant Chemotherapy In Ca Cervix**

## **Clinical trials**

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# INTRODUCTION

- Cervical cancer is a global public health challenge. It is the second most common cancer in women and third cause of death from malignant diseases in women worldwide.
- For early-stage cervical cancer, radical surgery is accepted as the standard treatment.
- However, there is still variable opinions on the best approach for bulky ( $\geq 4$  cm) tumour .
- The survival rate of patients with early-stage cervical cancer is 80–90% in non-bulky tumors, but decreases to 50–60% in bulky tumors.

## Cont.....

- Though Platinum based chemoradiation (CRT) has been the standard treatment for patients with locally advanced disease since 1999 ,further improvement in outcome is desirable in these patients.
- Therefore, a new therapeutic modality targeted to LACC should be developed.
- Neoadjuvant chemotherapy (NAC) prior to surgery or radiotherapy has been applied as a new therapeutic strategy for bulky or locally advanced disease.
- Neoadjuvant chemotherapy (NACT) plays yet an unproved role in cervical cancer treatment, particularly when followed by CRT, where data is scarce.

# RATIONALE OF USING NACT

- **Tumor-size reduction** : facilitate subsequent local therapy. This reduction can transform inoperable tumors into radically resectable ones.
- **Increase radio sensitivity** and decrease the hypoxic cell fraction.
- **Treats the micro metastatic disease**, preventing a significant proportion of relapses.
- Identified as an **important prognostic factor** in several studies.
- **Reduces lymph node and parametrial invasion.**

# AGENTS USED IN NACT

- Cisplatin : most active platinum agent, RR 20%
- Ifosfamide: 20% RR at a dose 1.2gm /m<sup>2</sup> for 5 days
- Cis-Ifos combo : RR (31%/17.8%), no OS benefit
- Anthracycline : RR 20%, Cardiotoxic
- Taxane: RR 17%
- Paclitaxel-Carboplatin: hematotoxic, Myelosuppression

Authors	Publication	Number	Stage	Comparison	Response rate
Friedlander [27]	1983	35	IIB	cisplatin (60 mg/m <sup>2</sup> day1), vinblastine (4 mg/m <sup>2</sup> , days 1 and 2), and bleomycin (15 mg, days 1, 8, and 15) followed by radiation therapy and/or surgery	66% (complete response 18%)
Lara [29]	1990	26	IIIB	cisplatin (20 mg/m <sup>2</sup> on day 1-5) and ifosfamide (1.5 g/m <sup>2</sup> on day 1-5)	62.5%
Hwang [28]	2001	80	IB-IIIB	cisplatin (50 mg/m <sup>2</sup> day1), vinblastine (4 mg/m <sup>2</sup> , days 1), and bleomycin (16 mg/m <sup>2</sup> , days1, 2)	93.7% (complete response 50%)
Park [19]	2004	43	IB-IIIB	paclitaxel (60 mg/m <sup>2</sup> , day 1) and cisplatin (60 mg/m <sup>2</sup> , day 1)	90.7%
Buda [30]	2005	113	IB-IV	cisplatin 75 mg/m <sup>2</sup> paclitaxel 175 mg/m <sup>2</sup> ifosfamide 5 g/m <sup>2</sup>	48%
Bae [32]	2008	112	IB-IIIB	cisplatin (60 mg/m <sup>2</sup> , days 1, 2) and etoposide (100 mg/m <sup>2</sup> , day 1)	69.7%
Helena [31]	2010	141	IB	cisplatin (75 mg/m <sup>2</sup> ) and ifosfamide (2 g/m <sup>2</sup> )	69.5%

**Table 1.** Pilot study of neoadjuvant chemotherapy for cervical cancer

Gynecologic Oncology Group (GOG) randomized trials with cisplatin-based doublets in advanced cervical carcinoma

	GOG-110 [9]		GOG-169 [10]		GOG-179 [11]	
	Cisplatin	Cisplatin+ ifosfamide	Cisplatin	Cisplatin+ paclitaxel	Cisplatin	Cisplatin+ topotecan
RR (%)	19	31*	19	36*	13	27 <sup>a</sup>
PFS (mo)	3.2	4.6*	2.8	4.8*	2.9	4.6 <sup>a</sup>
OS (mo)	8	8.3	8.8	9.7	6.5	9.4 <sup>a</sup>

RR: response rate; PFS: progression-free survival; OS: overall survival.

<sup>a</sup> Statistically significant difference.

(Strongly consider clinical trial)

**First-line combination therapy**

- Cisplatin/paclitaxel<sup>1,2</sup>
- Carboplatin/paclitaxel<sup>3</sup>
- Cisplatin/topotecan<sup>4</sup>
- Cisplatin/gemcitabine (category 2B)<sup>5</sup>

**Possible first-line single agent therapy**

- Cisplatin (preferred as a single agent)<sup>2</sup>
- Carboplatin<sup>6</sup>
- Paclitaxel<sup>7</sup>

**Second-line therapy<sup>††</sup>**

(Agents listed are category 2B unless otherwise noted)

- Bevacizumab
- Docetaxel
- 5-FU (5-fluorouracil)
- Gemcitabine
- Ifosfamide
- Irinotecan
- Mitomycin
- Topotecan
- Pemetrexed (category 3)
- Vinorelbine (category 3)

# Dose of chemotherapy and interval of cycles in NACT

Table 1

Overall survival (OS) by frequency of chemotherapy and cisplatin dose intensity in comparison 1 [6]

Variable	Trials	HR (95% CI)	<i>p</i> value	Heterogeneity <i>p</i> value	5-year OS
<i>Frequency of chemotherapy</i>					
>14 days	11	1.25 (1.07–1.46)	0.005	0.23	↓8%
≤14 days	6	0.76 (0.62–0.92)	0.005	0.19	↑7%
<i>Cisplatin dose intensity</i>					
<25 mg/m <sup>2</sup>	7	1.35 (1.11–1.64)	0.002	0.74	↓11%
≥25 mg/m <sup>2</sup>	11	0.91 (0.78–1.05)	0.2	0.001	↑3%

Neoadjuvant chemotherapy  
for locally advanced disease:  
Meta-analysis (2004): MRC (UK) group

- 18 trials
- IPD meta-analysis
- Included stage IB-IV disease
- Did not include trials with concurrent chemoradiotherapy  
NACT → Local therapy vs Local therapy alone
- N=2074
- Significant survival benefit for NACT with cycles duration <14 days and using Cisplatin @ >25 mg/m<sup>2</sup>/week
- No effect of age, stage, histology, grade and nodal involvement

Tierney et al. Cochrane Database

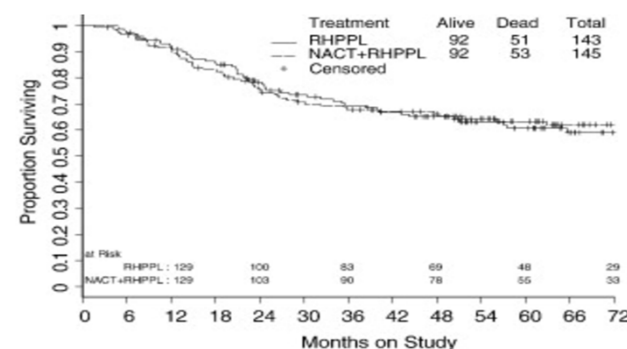
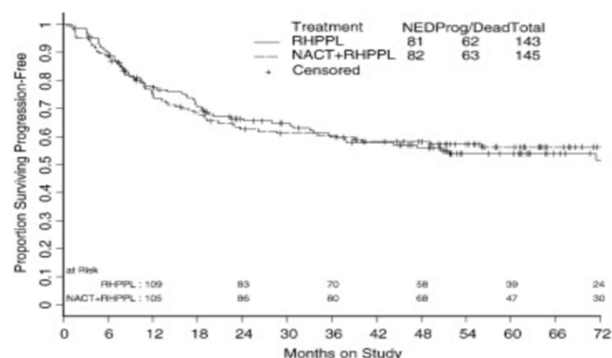
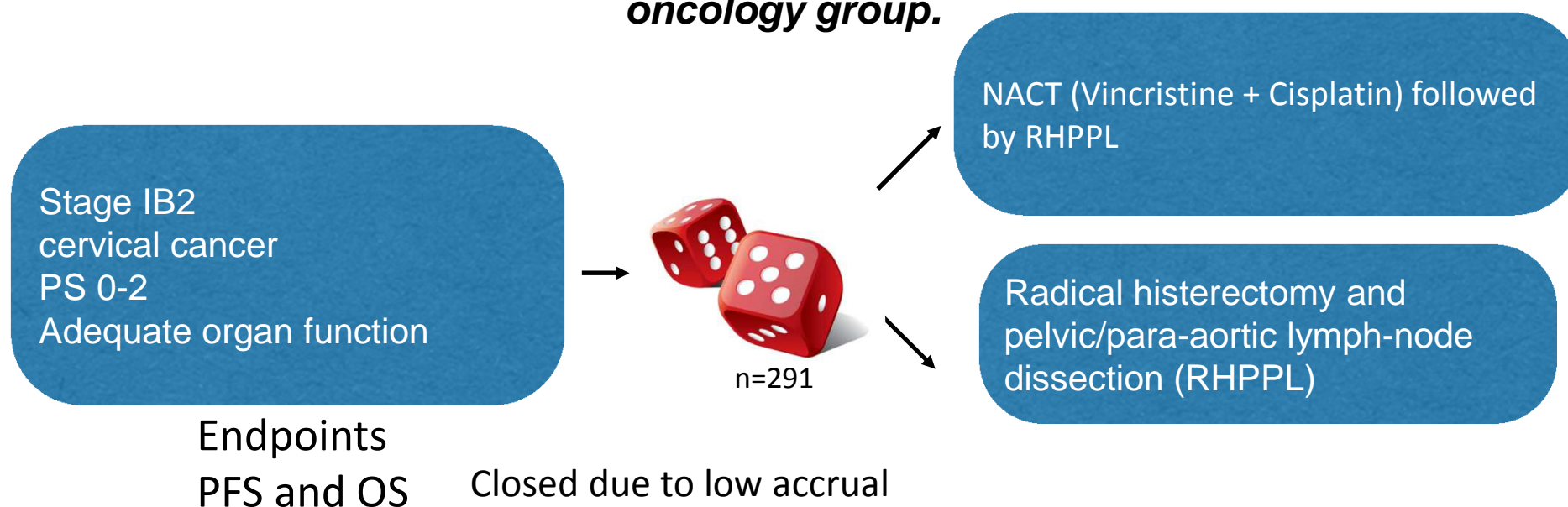
As a result, a short interval and a high dose of cisplatin appear to offer a great advantage for survival in cervical cancer patients.

Clinical research on the efficacy of NAC

- Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer
- Neoadjuvant chemotherapy plus radical surgery versus radiation therapy
- Neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone
- Neoadjuvant chemotherapy plus radical surgery versus surgery only and concurrent chemo radiation therapy only
- Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy

**Neoadjuvant chemotherapy plus surgery versus  
surgery for cervical cancer**

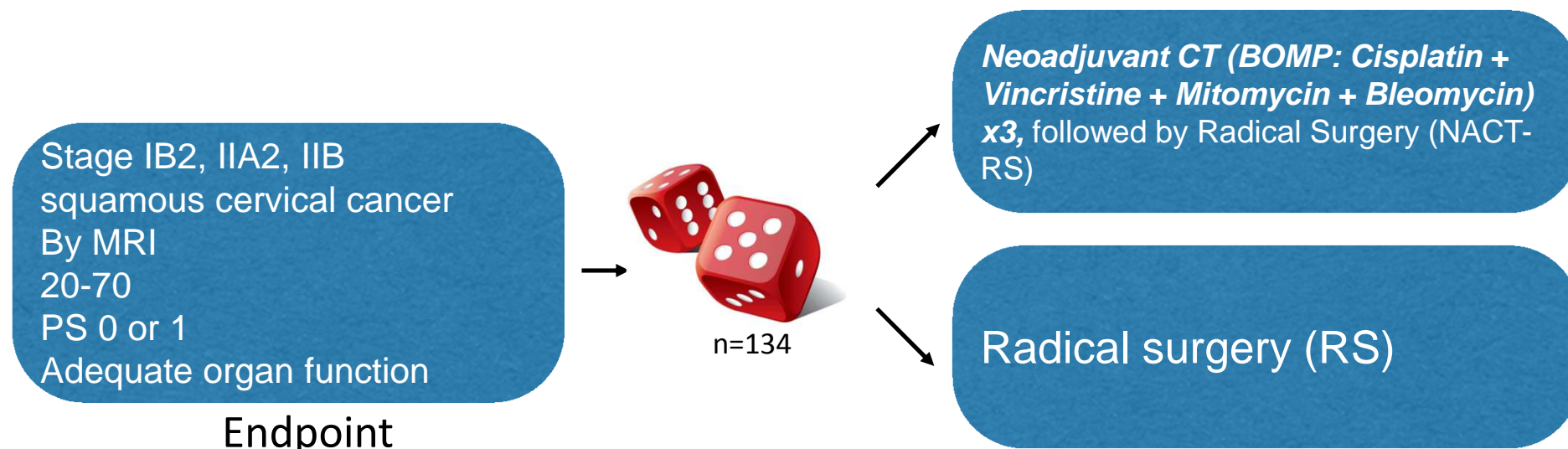
**GOG-141: Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group.**



Eddy, G. L., Bundy, B. N., Creasman, W. T., Spirtos, N. M., Mannel, R. S., Hannigan, E., & O'Connor, D. (2007). Treatment of (?bulky?) stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: A phase III trial of the gynecologic oncology group. *Gynecologic Oncology*, 106(2), 362–369.

<https://doi.org/10.1016/j.ygyno.2007.04.007>

***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)***



Endpoint  
OS  
***Post surgical RT if high risk pathology after RS***

**Pelvic lymph node metastasis,  
parametrial involvement,  
or deep stromal invasion ( $\geq 2/3$ ).**

Katsumata, N., Yoshikawa, H., Kobayashi, H., Saito, T., Kuzuya, K., Nakanishi, T., ... Japan Clinical Oncology Group. (2013). 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). *British Journal of Cancer*, 108(10), 1957–63.

<https://doi.org/10.1038/bjc.2013.179>

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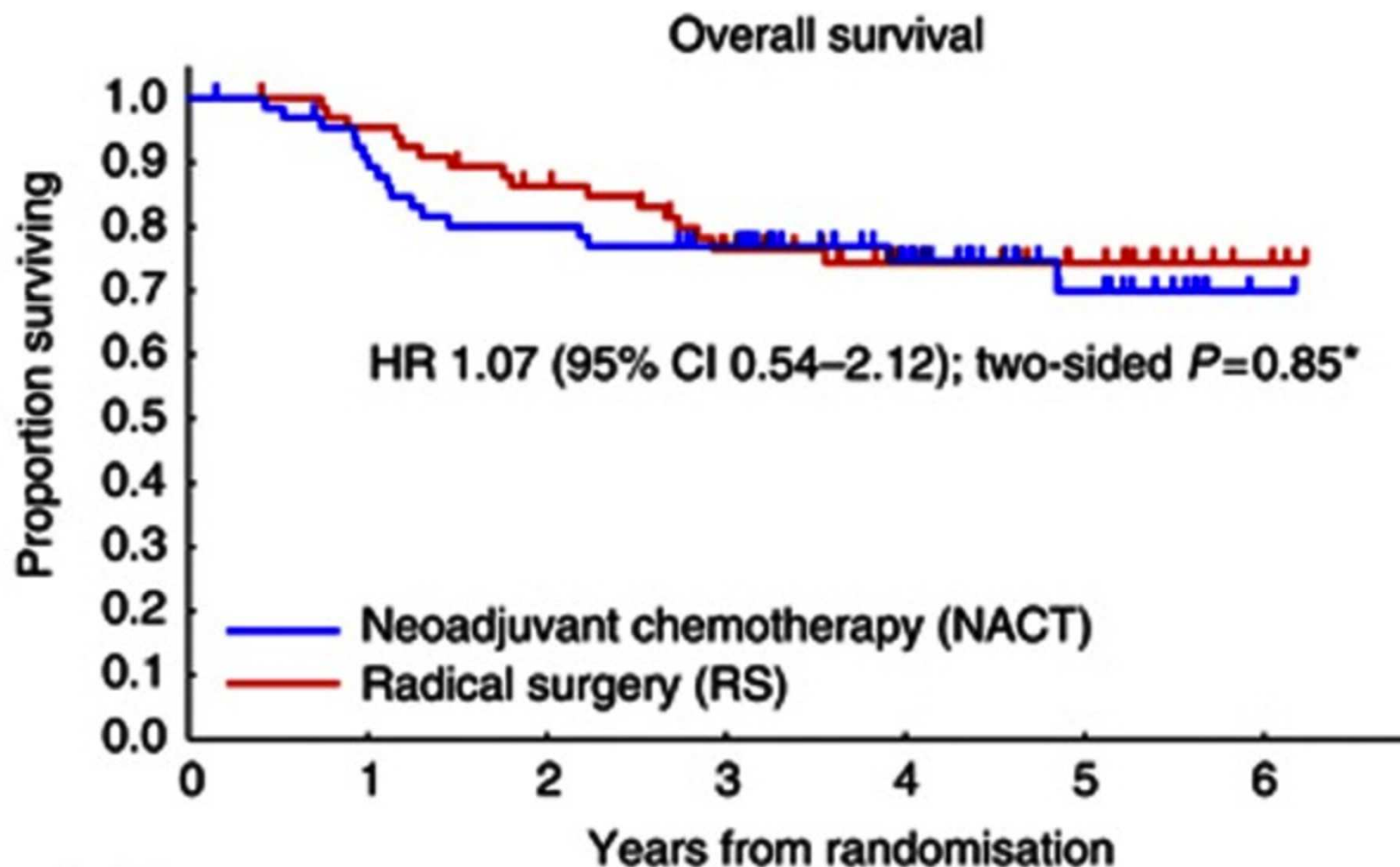
**Clinical response of neoadjuvant chemotherapy**

<b>Response category</b>	<b>Investigator assessment(n=67)</b>	<b>Independent central review(n=67)</b>
CR	9 (13)	8 (12)
PR	38 (57)	36 (54)
SD	18 (27)	20 (30)
PD	0 (0)	0 (0)
NE	1 (1)	2 (3)
<b>Overall response</b>	<b>47 (70)</b>	<b>44 (66)</b>
95% CI	58–81	53–77

Katsumata, N., Yoshikawa, H., Kobayashi, H., Saito, T., Kuzuya, K., Nakanishi, T., ... Japan Clinical Oncology Group. (2013). 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). *British Journal of Cancer*, 108(10), 1957–63.

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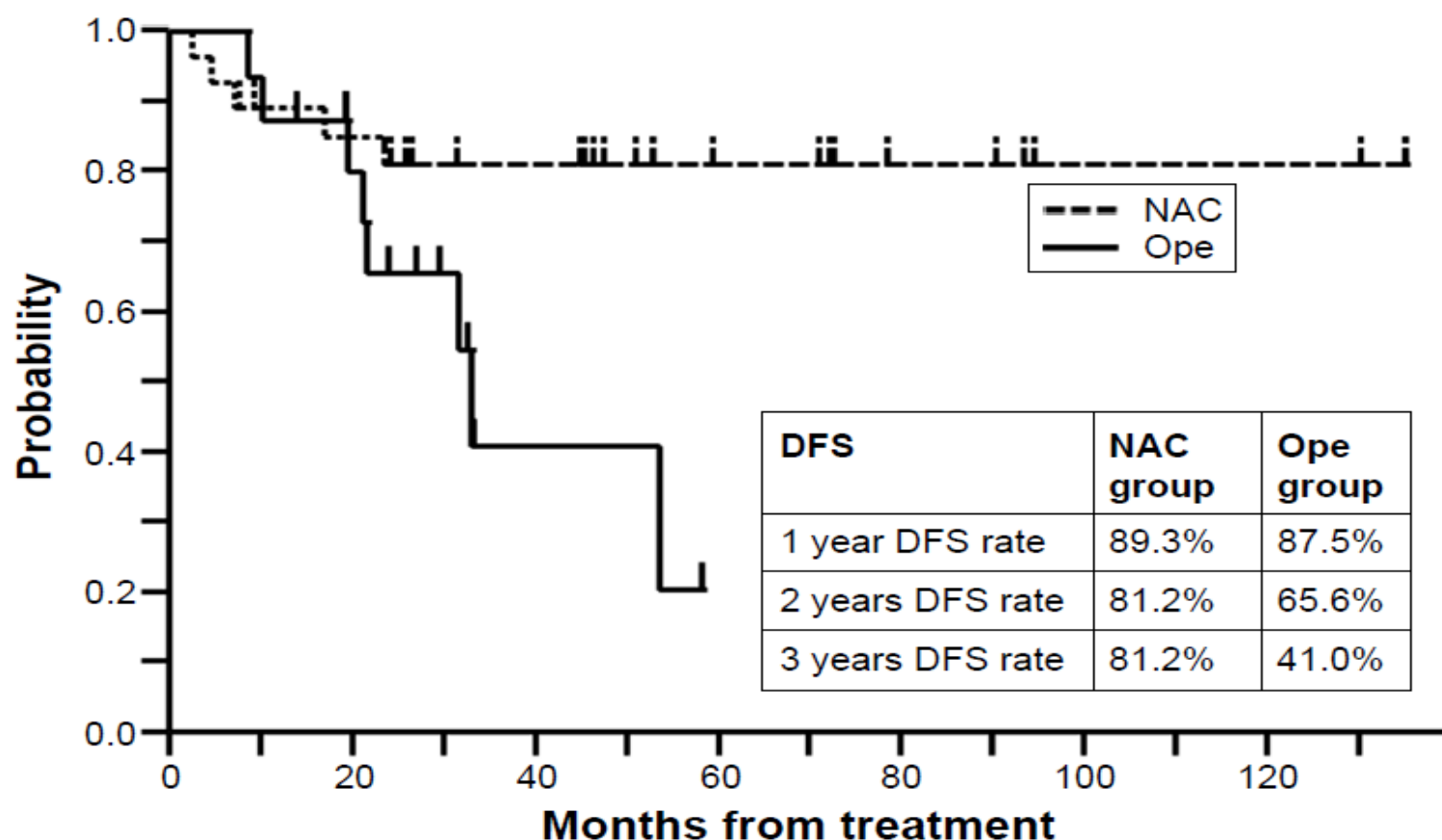
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<https://doi.org/10.1038/bjc.2013.179>

# A retrospective study of neoadjuvant chemotherapy plus radical hysterectomy versus radical hysterectomy alone in patients with stage II cervical squamous cell carcinoma presenting as a bulky mass



# Original Article

## Clinical efficacy and safety of paclitaxel plus carboplatin as neoadjuvant chemotherapy prior to radical hysterectomy and pelvic lymphadenectomy for Stage IB<sub>2</sub>-IIB cervical cancer

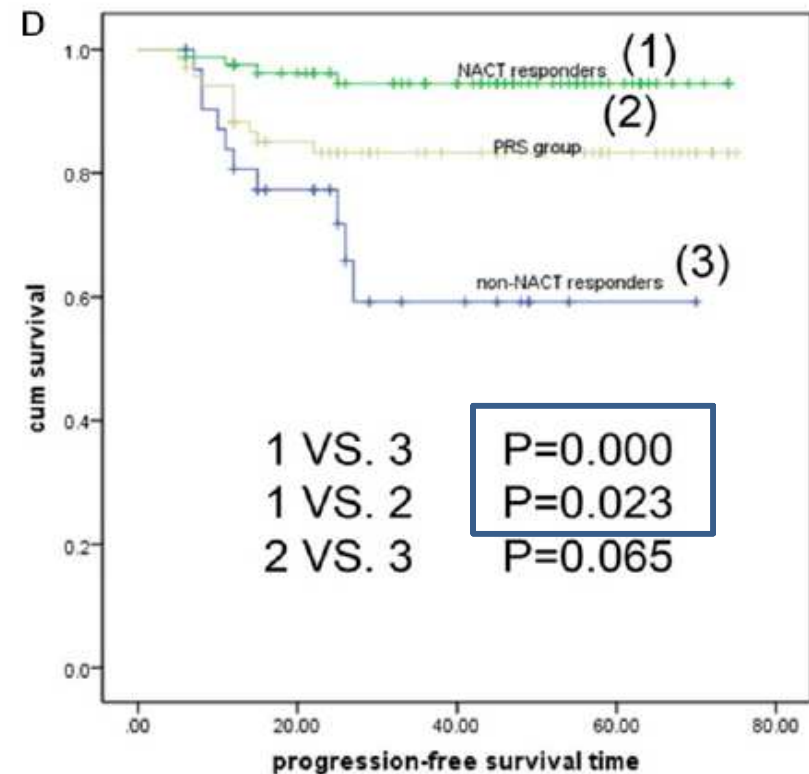
Lu Yang\*, Jianfeng Guo\*, Yi Shen, Jing Cai, Zhoufang Xiong, Weihong Dong, Jie Min, Zehua Wang

**Table 3** Operative details

Characteristics	NAC group (n=28)	Ope group (n=17)	P-value
Type of surgery <sup>a</sup>			
RH	28	17	NA
Other	0	0	
Time (minutes) <sup>b</sup>			
Median (IQR)	245 (210–309)	260 (231–303)	0.582
Blood loss (mL) <sup>b</sup>			
Median (IQR)	484 (391–857)	555 (365–806)	0.797
Blood transfusion <sup>a</sup>			
Yes	4	3	0.763
No	24	14	
Time from surgery to discharge (days) <sup>b</sup>			
Median (IQR)	18 (14–25)	25 (21–34)	0.032

**Notes:** <sup>a</sup>Chi-square test. <sup>b</sup>Mann–Whitney U-test.

**Abbreviations:** NAC, neoadjuvant chemotherapy; RH, radical hysterectomy; NA, not applicable; IQR, interquartile range.

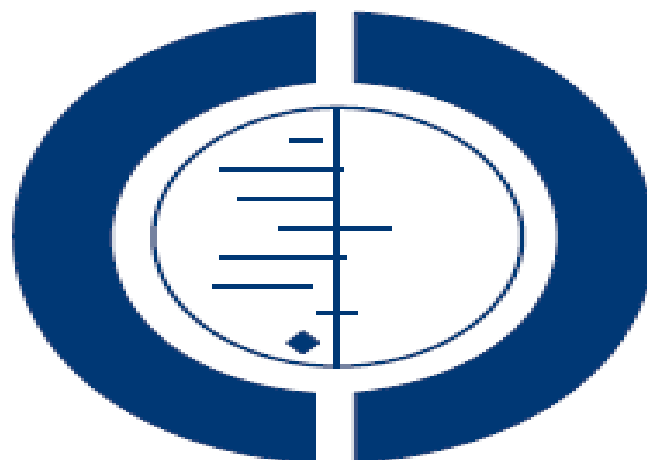


Rydzewska L, Tierney J, Vale CL, Symonds PR

TheCochrane Library 2010, Issue 1

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

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



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# STUDY DESIGN

- Early or locally advanced cervical cancer who had not undergone any prior treatment likely to interfere with the treatment comparison.  
Six trials (1072 women) were identified for inclusion in the review
- Trials giving radical radiotherapy for inoperable tumours and/or post-operative radiotherapy were also eligible.
- Neoadjuvant chemotherapy followed by radical surgery versus radical surgery
- The primary outcome was overall survival (OS).
- Secondary outcomes were progression-free survival (PFS), local and distant recurrence, rates of resection and surgical morbidity.

**Table 1** Demographic characteristics of 6 RCT studies

Author	FIGO stage	Histology	Comparison (No. of patients)	Regimen of NAC	Cycles of NAC
Sardi (1997) (12)	IB	SCC	NCS + RT [102] Surgery + RT [103]	CDDP 50 mg/m <sup>2</sup> day 1 VCR 1 mg/m <sup>2</sup> day 1 BLM 25 mg/m <sup>2</sup> day 1-3	Every 10 days for 3 cycles
Napolitano (2003) (13)	IB-IIIB	SCC	NCS ± RT [106] Surgery ± RT [86]	CDDP 50 mg/m <sup>2</sup> day 1 VCR 1 mg/m <sup>2</sup> day 1 BLM 25 mg/m <sup>2</sup> day 1-3	Every 21 days for 3 cycles
Cai (2006) (14)	IB	SCC AD	NCS ± RT [52] Surgery ± RT [54]	CDDP 75 mg/m <sup>2</sup> day 1 5-FU 24 mg/kg day 1-5	Every 21 days for 2 cycles
Katsumata (2006) (5)	IB2-IIIB	SCC	NCS ± RT [29] Surgery ± RT [33]	BLM 7 mg/m <sup>2</sup> day 1-5 VCR 0.7 mg/m <sup>2</sup> day 5 MMC 7 mg/m <sup>2</sup> day 5 CDDP 14 mg/m <sup>2</sup> day 1-5	Every 21 days for 2 cycles
Eddy (2007) (23)	IB2	SCC AD, ASC	NCS ± RT [145] Surgery ± RT [143]	CDDP 50 mg/m <sup>2</sup> day 1 VCR 1 mg/m <sup>2</sup> day 1	Every 10 days for 3 cycles
Chen (2008) (24)	IB2-IIIB	SCC AD, ASC	NCS ± RT [72] Surgery ± RT [70]	CDDP 100 mg/m <sup>2</sup> day 1 MMC 4 mg/m <sup>2</sup> day 1-5 5-FU 24 mg/kg day 1-5	Every 14 days for 2-3 cycles

RCT, randomized controlled trial; FIGO, Federation of Gynecology and Obstetrics; NAC, neoadjuvant chemotherapy; SCC, squamous cell carcinoma; NCS, neoadjuvant chemotherapy followed by surgery; RT, radiotherapy; VCR, vincristine; BLM, bleomycin; AC, adenocarcinoma; ASC, adenosquamous carcinoma; 5-FU, 5-fluorouracil; MMC, MitomycinC.

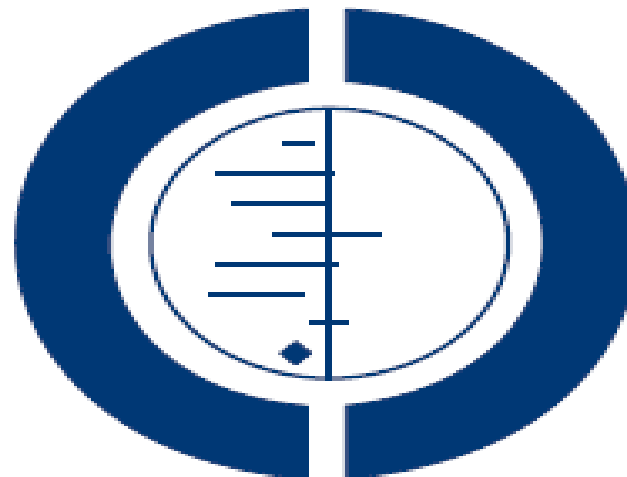
- PFS was significantly improved with NACT (HR=0.76, 95% CI=0.62to0.94, p=0.01)
- No OS benefit was observed (HR=0.85, 95% CI=0.67to1.07, p=0.17).
- Both local (OR = 0.76, 95% CI = 0.49 to 1.17, p = 0.21) and distant (OR = 0.68, 95% CI = 0.41 to 1.13, p = 0.13) recurrence and rates of resection (OR=1.55,95%CI=0.96to2.50,p=0.07) only tended to be in favor of neoadjuvant chemotherapy
- Exploratory analyses of pathological response showed a significant decrease in adverse pathological findings with neoadjuvant chemotherapy (OR = 0.54, 95% CI = 0.39 to 0.73, p = < 0.0001 for lymph node status; OR = 0.58, 95% CI = 0.41 to 0.82, p = 0.002 for parametrial infiltration) which despite a high level of heterogeneity was still significant when the random effects model was used.
- There was also no difference in the effect of neoadjuvant chemotherapy according to total cisplatin dose, chemotherapy cycle length or by cervical cancer stage.

**Neoadjuvant chemotherapy plus radical  
surgery versus radiation therapy**

# META – ANALYSIS (2004): MRC (UK) group

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

**Tierney J, Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration  
(NACCCMA) Collaboration, Rydzewska L.**





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# Neoadjuvant chemotherapy for locally advanced disease: Meta-analysis (2004): MRC (UK) group

- IPD meta-analysis
- Included stage IB-IV disease
- Did not include trials with concurrent chemoradiotherapy

## Objectives

- Neoadjuvant chemotherapy  surgery Vs radiotherapy.
- Neoadjuvant chemotherapy  radical radiotherapy Vs radiotherapy.

## NACT→ Surgery vs RT:

- 5 trials
- N=872
- A significant improvement in 5-year OS (14%) and DFS (13%)
- No change based on age, stage, histology, grade and nodal status

## **Defining the Role of Neoadjuvant Chemotherapy Followed by Surgery in Locally Advanced Cancer Cervix: A Meta-analysis of Phase III Trials.**

Osman MA

### **STUDY OBJECTIVES:**

This meta-analysis was performed to compare the outcomes between NACT-S and RT for locally advanced cancer cervix.

### **RESULTS:**

Data were collected from 1171 patients enrolled in seven phase III trials.

The 5-year PFS (progression-free survival) for NACT-S and RT were 62 and 45.5 %, respectively.

The 5-year OS for NACT-S and RT were 66 and 49 %, respectively.

**NACT-S was associated with better late toxicities compared to RT.**

### **CONCLUSION:**

NACT-S is a reasonable treatment option for locally advanced cancer cervix. It achieved better results than RT, especially for stages from IB2 to IIB.

# Conclusions

- The meta-analysis suggested that NACT followed by surgery improves overall survival compared with nonstandard radiotherapy.
- However the control arm (radiotherapy alone) should be compared with the current standard of care of chemo radiotherapy for the adoption of NACT before surgery or RT as the standard of care.

**Neoadjuvant chemotherapy followed by radiotherapy  
versus radiotherapy alone**

## **Neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced carcinoma cervix: a prospective randomized study.**

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# Neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced carcinoma cervix: a prospective randomized study

## Study Objective:

- To compare the **disease response**, disease free survival, overall survival and toxicity profile to neoadjuvant chemotherapy followed by radiotherapy(CT-RT group) versus radiotherapy alone(RT alone) in locally advanced carcinoma cervix.

## Materials and Method:

- **July 2007 and August 2008**, 113 patients with squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma cervix, FIGO stage IIB-IIIB,
- Two cycles of cisplatin and 5- fluorouracil(CT) followed by radiotherapy(RT) (CT-RT group,n=58) or RT alone (RT alone group , n=55).

- Inj cisplatin : 50mg/m<sup>2</sup> on day 1 and 2 in divided doses. The drug was given in an infusion over a period of 90minute after adequate hydration and antiemetic followed by mannitol diuresis.
- 5fluorouracil :- It was given in a dose of 500mg/m<sup>2</sup> over 6 hours on day 1 and day 2 repetition 3 weekly, total 2 cycles .
- Radiotherapy:
- Started within one week of randomization or within 2-3 weeks of completing the second cycle of chemotherapy. RT treatment was same in both arms. External beam radiation therapy was administered using cobalt 60 teletherapy machine.
- A dose of 45 Gy in 20 fractions in 4 weeks was given at a dose of 225 centi gray per fraction daily, for 5 days in a week.
- After a gap of 1 to 2 weeks patients were reassessed for response and patient with good local response , intracavitary brachytherapy using Selectron remote controlled LDR system, 137Cs based, giving a dose of 35 Gy to point A.

*Result & Conclusion: In the CT-RT group 54 evaluable patients 52 responded: clinical complete response(cCR) in 1(1.85%) and partial response in 51(94.45%). Remaining 2 patients (3.70%) had progressive disease (PR). Of 52 patients completed RT as planned. Following RT 38(73.08%) achieved clinical CR, 13(25%) had residual disease, and 1(1.92%) had progressed at first follow up after 1 month. The stage of disease, histological grade, had no influence on the response to CT. Nausea /vomiting were the major side effects of CT. In the RT group, 54 patients were evaluable 41(75.93%) patients achieved clinical CR, 12(22.22%) had residual disease, and 1(1.85%) progressed. The side effects of RT were lower GI toxicity (diarrhea) and local skin reaction. These were equally distributed between the two groups. After 36 months of follow up, cCR was seen in 34(64.15%) patients, PR in 8(15.09%) patients and 11(20.76%) patients had died in CT-RT group. In RT alone group 36(66.67%) patients had cCR, 8(14.82%) patients had PD and 10 (18.51%) patients had died. There were no significant difference in overall and disease free survival in the two groups.*

## NACT followed by radiotherapy: updates

- Seven prospective RCTs were conducted comparing radiotherapy alone with NACT followed by radiotherapy
- Unfortunately, of these seven trials, five demonstrated no benefit from neoadjuvant therapy, and two demonstrated a significantly better survival rate with radiotherapy alone.
- None of these trials compared NACT followed by radiotherapy with concurrent chemoradiation.

**TABLE 3** Randomized trials of neoadjuvant chemotherapy followed by radiation versus radiation alone

Author	Treatment	Patients	Stages	% Survival	p
Tattersall (21)	Epirubicin 110 mg/m <sup>2</sup> , CDDP 60 mg/m <sup>2</sup> (3 cycles) vs RT	129 vs 131	IIB–IVA	50 vs 70 @ 3y	0.02*
Souhami (22)	Bleomycin 120 mg/m <sup>2</sup> , vincristine 1 mg/m <sup>2</sup> , mitomycin C 10 mg/m <sup>2</sup> and CDDP 50 mg/m <sup>2</sup> (3 cycles) + RT vs RT	39 vs 52	IIIB	23 vs 39 @ 5y	0.02*
Kumar (23)	Bleomycin 15 mg/m <sup>2</sup> , ifosfamide 1 g/m <sup>2</sup> days 1–5 and CDDP 50 mg/m <sup>2</sup> (2 cycles) + RT vs RT	94 vs 90	IIB–IVA	38 vs 43 @ 3y	NS
Tattersall (24)	CDDP 50 mg/m <sup>2</sup> , vinblastine 10 mg/m <sup>2</sup> and bleomycin 120 mg/m <sup>2</sup> (3 cycles) + RT vs RT	34 vs 37	IIB–IVA	40 vs 45 @ 5y	NS
Chauvergne (25)	Methotrexate 10 mg/m <sup>2</sup> , chlorambucil 20 mg/m <sup>2</sup> , vincristine 0.2 mg/m <sup>2</sup> and CDDP 80 mg/m <sup>2</sup> , (2 cycles) + RT vs RT	75 vs 76	IIB–III	59 vs 54 @ 3y	NS
Sundfær (26)	CDDP 100 mg/m <sup>2</sup> , 5-FU 1 g/m <sup>2</sup> (3 cycles) + RT vs RT	47 vs 47	IIIB–IVA	36 vs 39 @ 5y	NS
Leborgne (27)	CDDP 50 mg/m <sup>2</sup> days 1–3, vincristine 1 mg/m <sup>2</sup> days 1–3, bleomycin 25 mg/m <sup>2</sup> , days 1–3 (3 cycles of 10 d) + RT vs RT	48 vs 48	IB2–IVA	38 vs 45 @ 5y	NS
Herod (28)	CDDP 50 mg/m <sup>2</sup> , ifosfamide 5 g/m <sup>2</sup> , bleomycin 30U (2 or 3 cycles) + RT vs RT	86 vs 86	IIB–IVA	31 vs 33 @ 5y	NS

Worst survival in arms receiving chemotherapy.

CDDP, cisplatin; 5-FU, fluorouracil; RT, external beam and brachytherapy.

**Neoadjuvant chemotherapy plus radical surgery versus surgery  
versus concurrent chemoradiation therapy only**



- Retrospective review of the follow-up reports of 476 patients with stage IB2-IIIB cervical cancer enrolled from 2000 to 2005
- patients treated with NACT followed by surgery showed significantly higher 5-year survival rates than both the radical surgery (OS: HR, 1.813;  $p = 0.0175$ ) and concurrent chemoradiation treatment (OS: HR, 3.157;  $p < 0.0001$ ) groups.
- In the NACT plus surgery group, NACT with a combination of paclitaxel and cisplatin (TP) chemotherapy improved the long-term disease-free survival (DFS) and OS compared NACT with a chemotherapy regimen of vincristine, bleomycin, and cisplatin (VBP) ( $p < 0.001$ ).

# Cont.....

- A tumor size of more than 4 cm caused a significant reduction in both the 5-year DFS and OS rates (HR, 1.762; 95% CI, 1.131–2.744;  $p = 0.0122$  and HR, 1.669; 95% CI, 1.164– 2.392;  $p = 0.0053$ , respectively).
- The limitation of this study is that a selection bias resulted because of the retrospective nature of the investigation.
- In terms of the proportion of patients with a tumor larger than 4 cm, a higher response rate was observed in the concurrent chemo radiotherapy group than in the NACT plus surgery group (77.7% vs 49.7%).

**Neoadjuvant chemotherapy plus radical surgery  
followed by chemotherapy**



## Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer

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### HIGHLIGHTS

- NACT + RS + adjuvant chemotherapy may be an option for locally advanced cervical cancer, in terms of survival.
- NACT + RS + adjuvant chemotherapy as initial treatment leaves radiotherapy in reserve should the patient relapse or non-response to chemotherapy.

Between 2000 and 2007, NACT (cisplatin 100 mg/m<sup>2</sup> and paclitaxel 175 mg/m<sup>2</sup>, 3 cycles every 3 weeks) plus surgery followed by 4 cycles of platinum-based adjuvant chemotherapy was performed by Angioli et al. The authors reported that the 5-year OS and DFS rates were 81% and 70%, respectively. The 5-year OS rates of cervical cancer patients with positive and negative lymph nodes were 75% and 88%, respectively. The authors showed that adjuvant chemotherapy after NACT and surgery could be useful for patients with LACC.

**Currently ongoing randomized trial**

**ClinicalTrials.gov**

***Neoadjuvant Chemotherapy Followed by Surgery Versus Concurrent Chemoradiation in Carcinoma of the Cervix (NACTcervix)***

**This study is currently recruiting participants.**

*Verified November 2015 by Sudeep Gupta, Tata Memorial Hospital*

**ClinicalTrials.gov Identifier: NCT00193739**

**Primary Outcome Measures:**

Disease Free Survival [ Time Frame: 5 years ]

**Secondary Outcome Measures:**

Over all survival [ Time Frame: 7 years ]

Over all survival will be calculated from the date of entry into the study to the date of death due to any cause or the last follow up visit.

Rate of Distant Metastases [ Time Frame: 7 years ]

Estimated Enrollment: 730

Study Start Date: September 2003

**Estimated Study Completion Date: December 2017 Estimated Primary Completion Date: December 2017 (Final data collection date for primary outcome measure)**

## *Comparing Study Between Concurrent Chemoradiation and New Combination Treatment in Cervical Cancer Patients (TGOCphaseIII)*

Thai Gynecologic Oncology Collaborative Group

**Collaborators:** National Research Council of Thailand Clinical Research Collaborative Network

**ClinicalTrials.gov Identifier:** **NCT01000415**

Primary Outcome Measures: Overall survival [ Time Frame: 9 Years ]

Secondary Outcome Measures: Comparing DFS [ Time Frame: 9 years ]

Estimated Enrollment: 824

Study Start Date: June 2009

Estimated Study Completion Date: June 2018

<u>Arms</u>	<u>Assigned Interventions</u>
Experimental: Cisplatin plus gemcitabine Experimental arm: NACT (cisplatin plus gemcitabine) followed by surgery Control arm: concurrent chemoradiation (cisplatin/carboplatin)during standard radiation	Cisplatin 50 mg/m2 (in the vein)on day 1 of each 23 day cycle plus gemcitabine 1000 mg/m2 on day 1 and day 8, for 3 cycles: until progression or unacceptable toxicity develops.

***EORTC 55994: Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO stage Ib2, IIa > 4 cm or IIb cervical cancer.***

***PI's: G. Kenter, S. Greggi, F. Landoni***

**Accrual (n = 626) completed June 2014**

Expected study completion = mid 2019

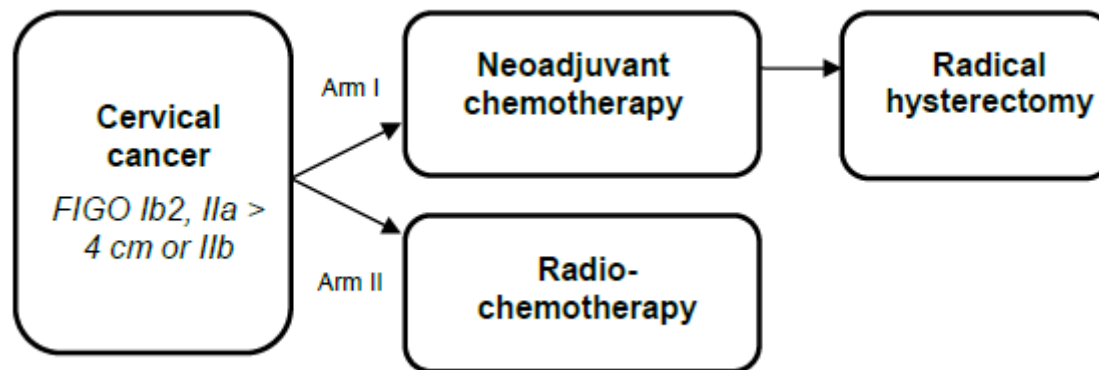
**Protocol amendment (v4.0):**

New primary end-point: OS at 5 years instead of OS

Secondary end-point: OS


Change of total number of patients: 625 (instead of 686)

Revised TR chapter



## Article in Press

### Phase II trial of neoadjuvant chemotherapy followed by chemoradiation in locally advanced cervical cancer☆

[Carla Rameri Alexandre Silva de Azevedo](#) [Luiz Cláudio Santos Thuler](#), [Maria Júlia Gonçalves de Mello](#), [Jurema Telles de Oliveira Lima](#), [Ana Luiza Fassizoli da Fonte](#), [Diógenes Fernando Santos Fontão](#), [Vandré Cabral Gomes Carneiro](#), [Tien Man Cabral Chang](#), [Carlos Gil Ferreira](#)

DOI: <http://dx.doi.org/10.1016/j.ygyno.2017.07.006>



Ib2–IVa were treated with neoadjuvant cisplatin 35 mg/m<sup>2</sup> and Gemciabine 1000 mg/m<sup>2</sup> D1 and D8, for 2 cycles. Then, they received CRT (50.4 Gy) with weekly Cisplatin 40 mg/m<sup>2</sup> followed by brachytherapy.

#### Results:

Between Sep/2013 and Oct/2015, 50 patients were initiated on NACT and CRT. RR was 81% at the end of treatment. PFS at 1 and 3-years were 73.4% and 53.9% respectively; and, OS at 1 and 3-years were 93.9% and 71.3% respectively.

**No overall response benefit on addition of NACT**



***Induction Chemotherapy Plus Chemoradiation VS Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer (INTERLACE)***

**This study is currently recruiting participants.**

*Verified June 2016 by University College, London*

**Sponsor:** University College, London

**Collaborator:** Cancer Research UK

**ClinicalTrials.gov Identifier:** **NCT01566240**

Primary Outcome Measures: Overall Survival [ Time Frame: 5 years ]

Secondary Outcome Measures: Progression free survival [ Time Frame: 12 weeks post treatment and then as required ]

Adverse events (AE): CTCAE v4.03

Quality of Life (UK and Ireland only) as assessed by EORTC QLQ-C30, QLQ-CX24 and EQ-5D

Patterns of first relapse (local and/or systemic) [ Time Frame: 12 weeks post treatment and as required ]

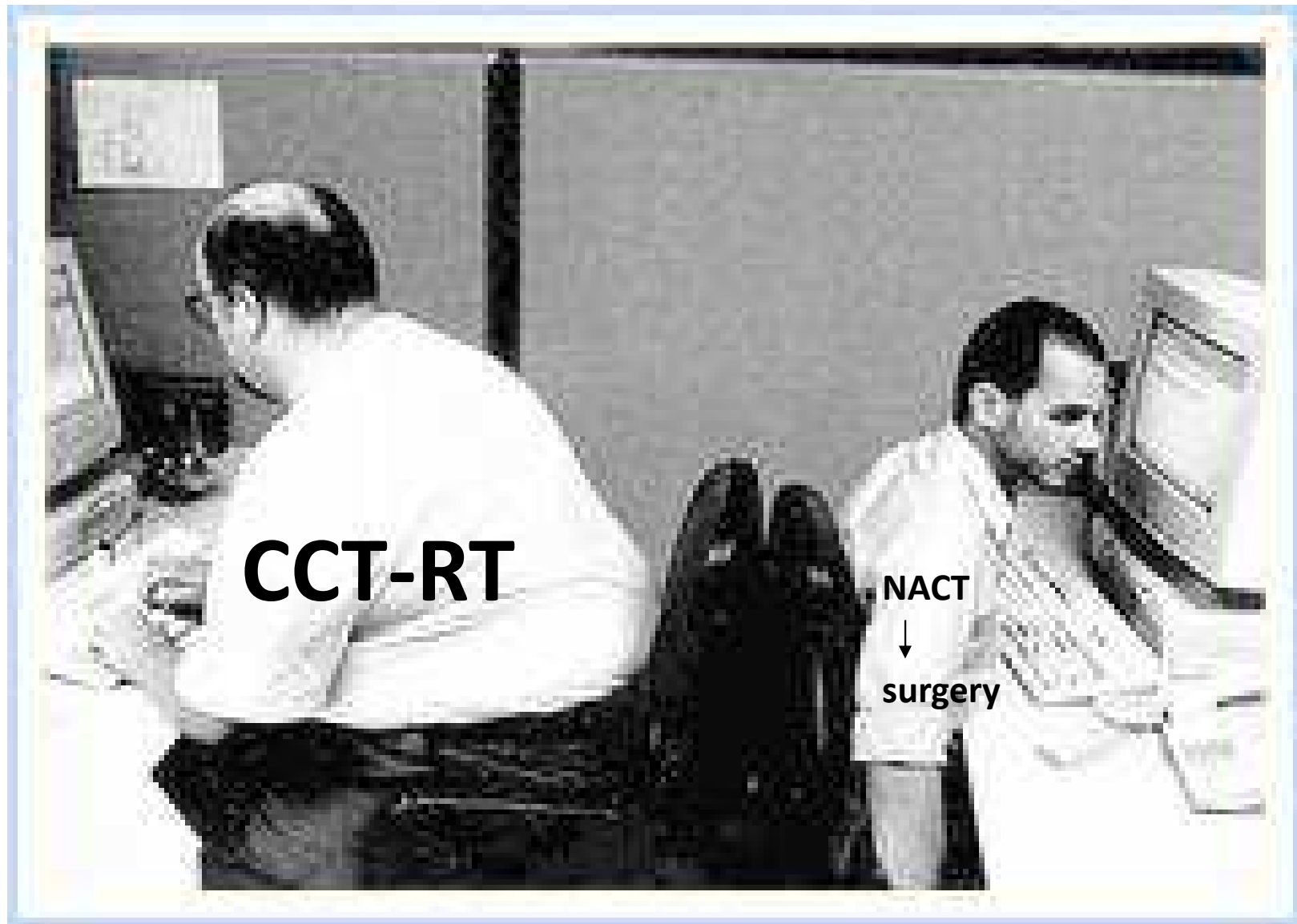
*Contd...*

Estimated Enrollment: 770

Study Start Date: September 2012

Estimated Study Completion Date: September 2021

<u>Arms</u>	<u>Assigned Interventions</u>
Active Comparator: Chemoradiation Radiotherapy (external beam and brachytherapy) plus concurrent Cisplatin weekly for 5 weeks	Radiation: Radiotherapy Radiotherapy comprising external beam 40-50.4Gy in 20-28 fractions plus intracavity brachytherapy to achieve a minimum total EQD2 dose of 78-86Gy. Drug: Cisplatin Cisplatin 40 mg/m2 (capped at 70mg total dose) weekly for five weeks maximum, commencing in the first week of radiotherapy or as soon as blood counts have recovered from induction chemotherapy.
Experimental: Induction Chemotherapy + Chemoradiation 6 cycles of weekly Paclitaxel and Carboplatin followed by Chemoradiation as per Active Comparator	Drug: Paclitaxel Paclitaxel 80 mg/m2 (capped at 160mg maximum total dose) weekly for 6 weeks i.e. on days 1, 8, 15, 22, 29 & 36. Drug: Carboplatin Carboplatin AUC 2 (capped at 270mg maximum total dose) weekly for 6 weeks i.e. on day 1, 8, 15, 22, 29, & 36. Chemo Radiotherapy: Same protocol

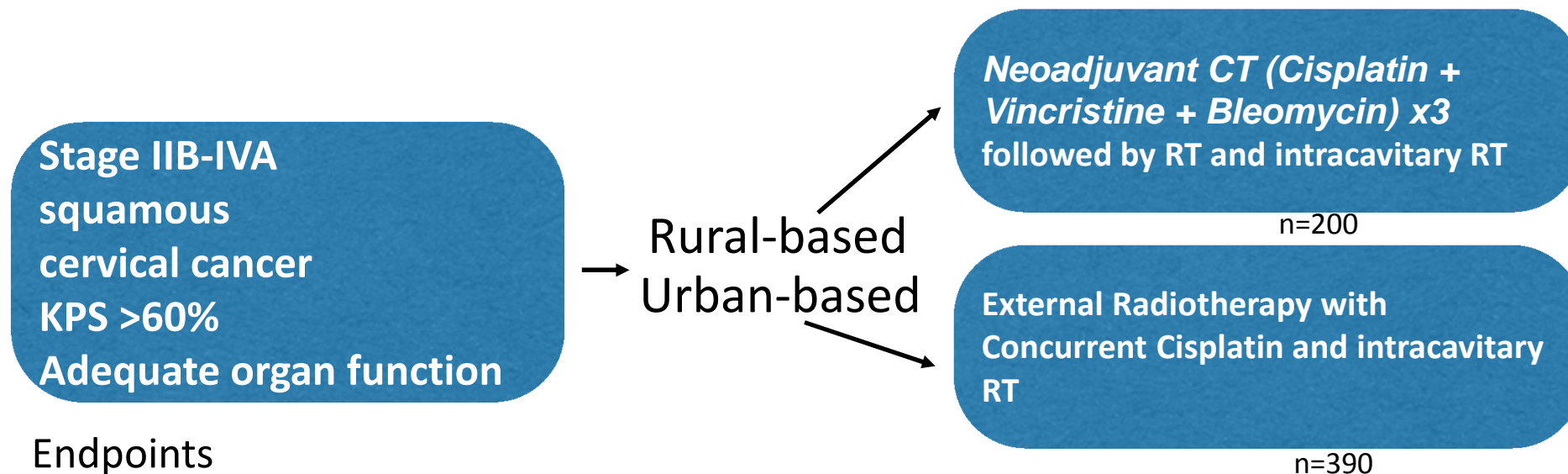


Postoperative pelvic EBRT with concurrent cisplatin-containing chemotherapy (category 1)<sup>140</sup> with (or without) vaginal brachytherapy is recommended for patients with positive pelvic nodes, positive surgical margin, and/or positive parametrium; these patients are considered to have “high-risk” disease (see *Adjuvant Treatment* in the NCCN Guidelines for Cervical Cancer). Vaginal brachytherapy may be a useful boost for those with positive vaginal mucosal margins. Adjuvant concurrent chemoradiation significantly improves overall survival for patients with high-risk, early-stage disease (those with positive pelvic nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy.<sup>140</sup> The Intergroup trial 0107/GOG 109 showed a statistically significant benefit of adjuvant pelvic radiation with concurrent cisplatin and 5-FU in the treatment of patients with stage IA2, IB, or IIA disease who had positive lymph nodes, positive margins, and/or microscopic parametrial involvement.

Cancer in the NCCN Guidelines) with (or without) individualized EBRT.<sup>187</sup>

Although neoadjuvant chemotherapy followed by surgery has been used in areas where RT is not available, data suggest no improvement in survival when compared with surgery alone for early-stage cervical cancer<sup>197-199</sup> or locally-advanced cervical cancer.<sup>200,201</sup> A meta-analysis of data on patients with stage IB1 to IIA cervical cancer found that neoadjuvant chemotherapy may reduce the need for adjuvant RT by decreasing tumor size and metastases, but indicated no overall survival benefit.<sup>201</sup> However, data from a second meta-analysis suggested that response to neoadjuvant chemotherapy was a strong prognostic factor for PFS and overall survival.<sup>202,203</sup> Outside of the clinical trial, the panel does not recommend the use of neoadjuvant chemotherapy.

Is neo-adjuvant chemotherapy a better option for management of cervical cancer patients of rural India?



## Endpoints

6-mo and 12-mo DCR (disease-control rate)

Complete Response in both arms

Stage	Number of patients	
	NACT Arm (Group A) (%)	Con. CT-RT Arm (Group B) (%)
II B	32/63 (50.8)	47/106 (44.3)
III A	17/21 (81)	32/34 (94)
III B	21/105 (20)	38/207 (18.4)
IV A	0	0
Total	70 (35)	117 (30)

Table 5: Patterns of relapse in both arms

Site of relapse	Group A (n=16) (%)	Group B (n=27) (%)	P value	RR (95% CI)
Local	14 (87.5)	25 (94.4)	0.619	1.156 (0.637-2.094)
Systemic	2 (12.5)	2 (7.4)		
Combined	0	0		

Dastidar, G. A., Gupta, P., Basu, B., Basu, A., Shah, J. K., & Seal, S. L. (2016). Is neo-adjuvant chemotherapy a better option for management of cervical cancer patients of rural India? Indian Journal of Cancer, 53(1), 56–9. <https://doi.org/10.4103/0019-509X.180826>

# CONCLUSION

- The role of neoadjuvant chemotherapy (NACT) in cervical cancer has been a matter of investigation over the last 20 years.
- NACT is feasible and produces impressive responses in cervical carcinoma, as has been demonstrated by several phase II , phase III trials and metaanalysis.
- Neoadjuvant chemotherapy plus surgery showed improved PFS and significant decrease in adverse pathological findings compared to surgery but no OS benefit . (Cochrane database 2010).
- NACT followed by surgery is a reasonable treatment option for locally advanced cancer cervix. It achieved better results than RT, especially for stages from IB2 to IIB. (Cochrane database 2004)

# Cont.....

- Neoadjuvant chemotherapy followed by radiotherapy didn't reveal any significant survival benefit compared to radiotherapy alone.
- In the 3-arm comparative study , patients treated with NACT followed by surgery showed significantly higher 5-year survival rates than both the radical surgery and concurrent chemoradiation treatment
- The role of adjuvant chemotherapy after NACT and surgery could be useful for the patients of LACC.
- But there are many drawbacks of NACT (prolonged Treatment periods , increased expenses, overmedication, tumor progression before surgery , radio resistance of cells) as explained in various studies.
- Furthermore the results of NACT till now are not convincing enough to accept it as a standard of care .
- The recent ongoing trials will probably strengthen the consensus regarding the use of this new approach .

# TAKE HOME MESSAGE....

- In our routine clinical practice, we should limit ourselves to standard treatment guidelines that are universally accepted.
- Experiments should only be done in the setting of a CLINICAL TRIAL.
- For locally advanced cancer cervix, **Concurrent chemoradiation is the current standard of care** and **NOT NACT followed by Surgery or Radiation.**

***Thank you***