Role of Neoadjuvant Chemotherapy In Ca Cervix

Clinical trials

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Kolkata
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 (≥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.
• 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 /m2 for 5 days
- Cis-Ifos combo: RR (31%/17.8%), no OS benefit
- Anthracycline: RR 20%, Cardiotoxic
- Taxane: RR 17%
- Paclitaxel-Carboplatin: hematotoxic, Myelosuppression
<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication</th>
<th>Number</th>
<th>Stage</th>
<th>Comparison</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedlander</td>
<td>1983</td>
<td>35</td>
<td>IIB</td>
<td>cisplatin (60 mg/m² day1), vinblastine (4 mg/m², days 1 and 2), and bleomycin (15 mg, days 1, 8, and 15) followed by radiation therapy and/or surgery</td>
<td>66% (complete response 18%)</td>
</tr>
<tr>
<td>Lara [29]</td>
<td>1990</td>
<td>26</td>
<td>IIIB</td>
<td>cisplatin (20 mg/m² on day 1-5) and ifosfamide (1.5 g/ m² on day 1-5)</td>
<td>62.5%</td>
</tr>
<tr>
<td>Hwang [28]</td>
<td>2001</td>
<td>80</td>
<td>IB-IIB</td>
<td>cisplatin (50 mg/m² day1), vinblastine (4 mg/ m², days 1), and bleomycin (16 mg/ m², days1, 2)</td>
<td><strong>93.7%</strong> (complete response 50%)</td>
</tr>
<tr>
<td>Park [19]</td>
<td>2004</td>
<td>43</td>
<td>IB-IIB</td>
<td>paclitaxel (60 mg/m², day 1) and cisplatin (60 mg/m², day 1)</td>
<td><strong>90.7%</strong></td>
</tr>
<tr>
<td>Buda [30]</td>
<td>2005</td>
<td>113</td>
<td>IB-IV</td>
<td>paclitaxel 175 mg/m2, ifosfamide 5 g/m2</td>
<td>48%</td>
</tr>
<tr>
<td>Bae [32]</td>
<td>2008</td>
<td>112</td>
<td>IB-IIB</td>
<td>cisplatin (60 mg/m², days: 1, 2) and etoposide (100 mg/m², day 1)</td>
<td>69.7%</td>
</tr>
<tr>
<td>Helena [31]</td>
<td>2010</td>
<td>141</td>
<td>IB</td>
<td>cisplatin (75 mg/m²) and ifosfamide (2 g/m²)</td>
<td>69.5%</td>
</tr>
</tbody>
</table>

**Table 1.** Pilot study of neoadjuvant chemotherapy for cervical cancer
Gynecologic Oncology Group (GOG) randomized trials with cisplatin-based doublets in advanced cervical carcinoma

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cisplatin</td>
<td>Cisplatin+</td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td>ifosfamide</td>
<td>paclitaxel</td>
<td>topotecan</td>
</tr>
<tr>
<td>RR (%)</td>
<td>19</td>
<td>31*</td>
<td>19</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>3.2</td>
<td>4.6*</td>
<td>2.8</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>8</td>
<td>8.3</td>
<td>8.8</td>
</tr>
</tbody>
</table>

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

* Statistically significant difference.
First-line combination therapy
- Cisplatin/paclitaxel
- Carboplatin/paclitaxel
- Cisplatin/topotecan
- Cisplatin/gemcitabine (category 2B)

Possible first-line single agent therapy
- Cisplatin (preferred as a single agent)
- Carboplatin
- Paclitaxel

Second-line therapy
(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)

(Strongly consider clinical trial)
Dose of chemotherapy and interval of cycles in NACT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trials</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>Heterogeneity p value</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;14 days</td>
<td>11</td>
<td>1.25 (1.07–1.46)</td>
<td>0.005</td>
<td>0.23</td>
<td>↓8%</td>
</tr>
<tr>
<td>≤14 days</td>
<td>6</td>
<td>0.76 (0.62–0.92)</td>
<td>0.005</td>
<td>0.19</td>
<td>↓7%</td>
</tr>
<tr>
<td><strong>Cisplatin dose intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 mg/m²</td>
<td>7</td>
<td>1.35 (1.11–1.64)</td>
<td>0.002</td>
<td>0.74</td>
<td>↓11%</td>
</tr>
<tr>
<td>≥25 mg/m²</td>
<td>11</td>
<td>0.91 (0.78–1.05)</td>
<td>0.2</td>
<td>0.001</td>
<td>↓13%</td>
</tr>
</tbody>
</table>
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/m²/week
- No effect of age, stage, histology, grade and nodal involvement

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.

Stage IB2 cervical cancer
PS 0-2
Adequate organ function

NACT (Vincristine + Cisplatin) followed by RHPPL

Radical histerectomy and pelvic/para-aortic lymph-node dissection (RHPPL)

Endpoints
PFS and OS

Closed due to low accrual

Stage IB2, IIA2, IIB squamous cervical cancer
By MRI
20-70
PS 0 or 1
Adequate organ function

Neoadjuvant CT (BOMP: Cisplatin + Vincristine + Mitomycin + Bleomycin) x3, followed by Radical Surgery (NACT-RS)

Radical surgery (RS)

Endpoint OS

Post surgical RT if high risk pathology after RS

Pelvic lymph node metastasis, parametrial involvement, or deep stromal invasion (≥2/3).

https://doi.org/10.1038/bjc.2013.179
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)

<table>
<thead>
<tr>
<th>Clinical response of neoadjuvant chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response category</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>NE</td>
</tr>
<tr>
<td><strong>Overall response</strong></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
</tr>
</tbody>
</table>


https://doi.org/10.1038/bjc.2013.179
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)


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 IB₂-IIB cervical cancer

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

Table 3 Operative details

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

Notes: ^aChi-square test. ^bMann–Whitney U-test.
Abbreviations: NAC, neoadjuvant chemotherapy; RH, radical hysterectomy; NA, not applicable; IQR, interquartile range.
Neoadjuvant chemotherapy for locally advanced cervix cancer (Review)

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

<table>
<thead>
<tr>
<th>Author</th>
<th>FIGO stage</th>
<th>Histology</th>
<th>Comparison (No. of patients)</th>
<th>Regimen of NAC</th>
<th>Cycles of NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardi (1997)</td>
<td>IB</td>
<td>SCC</td>
<td>NCS + RT [102] Surgery + RT [103]</td>
<td>CDDP 50 mg/m² day 1 VCR 1 mg/m² day 1 BLM 25 mg/m² day 1-3</td>
<td>Every 10 days for 3 cycles</td>
</tr>
<tr>
<td>Napolitano (2003)</td>
<td>IB-IIIB</td>
<td>SCC</td>
<td>NCS ± RT [106] Surgery ± RT [86]</td>
<td>CDDP 50 mg/m² day 1 VCR 1 mg/m² day 1 BLM 25 mg/m² day 1-3</td>
<td>Every 21 days for 3 cycles</td>
</tr>
<tr>
<td>Cai (2006)</td>
<td>IB</td>
<td>SCC</td>
<td>NCS ± RT [52] AD Surgery ± RT [54]</td>
<td>CDDP 75 mg/m² day 1 5-FU 24 mg/kg day 1-5</td>
<td>Every 21 days for 2 cycles</td>
</tr>
<tr>
<td>Katsumata (2006)</td>
<td>IB2-IIIB</td>
<td>SCC</td>
<td>NCS ± RT [29] Surgery ± RT [33]</td>
<td>BLM 7 mg/m² day 1-5 VCR 0.7 mg/m² day 5 MMC 7 mg/m² day 5 CDDP 14 mg/m² day 1-5</td>
<td>Every 21 days for 2 cycles</td>
</tr>
<tr>
<td>Eddy (2007)</td>
<td>IB2</td>
<td>SCC</td>
<td>NCS ± RT [145] AD, ASC Surgery ± RT [143]</td>
<td>CDDP 50 mg/m² day 1 VCR 1 mg/m² day 1</td>
<td>Every 10 days for 3 cycles</td>
</tr>
<tr>
<td>Chen (2008)</td>
<td>IB2-IIIB</td>
<td>SCC</td>
<td>NCS ± RT [72] AD, ASC Surgery ± RT [70]</td>
<td>CDDP 100 mg/m² day 1 MMC 4 mg/m² day 1-5 5-FU 24 mg/kg day 1-5</td>
<td>Every 14 days for 2-3 cycles</td>
</tr>
</tbody>
</table>

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=0.62 to 0.94, p=0.01)

• **No OS benefit was observed** (HR=0.85, 95% CI=0.67 to 1.07, 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=0.96 to 2.50, 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, radiation therapy, plus radical surgery versus radical surgery only.
Neoadjuvant chemotherapy for locally advanced cervix cancer (Review)

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

Tierney et al. Cochrane Database
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

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.

Dr Vikas Fotedar\textsuperscript{1}, Dr Rajeev K Seam\textsuperscript{2}, Dr Manoj K Gupta\textsuperscript{3}, Dr Anupam Jhobta\textsuperscript{4}.

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\textsuperscript{2}MD Radiotherapy, Prof \& HOD, Deptt. of Radiotherapy, IGMC, Shimla.
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\textsuperscript{4}MD Radiodiagnosis Asstt. Prof., Deptt of Radiodiagnosis, IGMC, Shimla.
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-flourouracil (CT) followed by radiotherapy (RT) (CT-RT group, n=58) or RT alone (RT alone group, n=55).
• **Inj cisplatin:** 50mg/m2 on day 1 and 2 in divided doses. The drug was given in an infusion over a period of 90 minutes after adequate hydration and antiemetic followed by mannitol diuresis.

• **5fluorouracil:** It was given in a dose of 500mg/m2 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>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Patients</th>
<th>Stages</th>
<th>% Survival</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tattersall</td>
<td>Epirubicin 110 mg/m², CDDP 60 mg/m² (3 cycles) vs RT</td>
<td>129 vs 131</td>
<td>IIB–IVA</td>
<td>50 vs 70 @ 3y</td>
<td>0.02*</td>
</tr>
<tr>
<td>Souhami</td>
<td>Bleomycin 120 mg/m², vincristine 1 mg/m², mitomycin C 10 mg/m² and CDDP 50 mg/m² (3 cycles) + RT vs RT</td>
<td>39 vs 52</td>
<td>IIIB</td>
<td>23 vs 39 @ 5y</td>
<td>0.02*</td>
</tr>
<tr>
<td>Kumar</td>
<td>Bleomycin 15 mg/m², ifosfamide 1 g/m² days 1–5 and CDDP 50 mg/m² (2 cycles) + RT vs RT</td>
<td>94 vs 90</td>
<td>IIB–IVA</td>
<td>38 vs 43 @ 3y</td>
<td>NS</td>
</tr>
<tr>
<td>Tattersall</td>
<td>CDDP 50 mg/m², vinblastine 10 mg/m² and bleomycin 120 mg/m² (3 cycles) + RT vs RT</td>
<td>34 vs 37</td>
<td>IIB–IVA</td>
<td>40 vs 45 @ 5y</td>
<td>NS</td>
</tr>
<tr>
<td>Chauvergne</td>
<td>Methotrexate 10 mg/m², chlorambucil 20 mg/m², vincristine 0.2 mg/m² and CDDP 80 mg/m² (2 cycles) + RT vs RT</td>
<td>75 vs 76</td>
<td>II–III</td>
<td>59 vs 54 @ 3y</td>
<td>NS</td>
</tr>
<tr>
<td>Sundfør</td>
<td>CDDP 100 mg/m², 5-FU 1 g/m² (3 cycles) + RT vs RT</td>
<td>47 vs 47</td>
<td>IIIB–IVA</td>
<td>36 vs 39 @ 5y</td>
<td>NS</td>
</tr>
<tr>
<td>Leborgne</td>
<td>CDDP 50 mg/m² days 1–3, vincristine 1 mg/m² days 1–3, bleomycin 25 mg/m², days 1–3 (3 cycles of 10 days) + RT vs RT</td>
<td>48 vs 48</td>
<td>IIB–IVA</td>
<td>38 vs 45 @ 5y</td>
<td>NS</td>
</tr>
<tr>
<td>Herod</td>
<td>CDDP 50 mg/m², ifosfamide 5 g/m², bleomycin 30U (2 or 3 cycles) + RT vs RT</td>
<td>86 vs 86</td>
<td>IIB–IVA</td>
<td>31 vs 33 @ 5y</td>
<td>NS</td>
</tr>
</tbody>
</table>

Worst survival in arms receiving chemotherapy.

CDDP, cisplatin; 5-FU, fluorouracil; RT, external beam and brachytherapy.
Neoadjuvant chemotherapy plus radical surgery versus surgery only versus concurrent chemoradiation therapy only
• Retrospective review of the follow-up reports of 476 patients with stage IB2-IIB 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).
• 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

Roberto Angioli a,b, Francesco Plotti a, Roberto Monter a, Alessia Aloisi a, Daniela Luvero a, Stella Capriglione a, Corrado Terranova a, Carlo De Cicco Nardone a, Ludovico Muzii a, Pierluigi Benedetti-Panici b

a Department of Obstetrics and Gynaecology, Campus Bio Medico University of Rome, Italy
b Department of Obstetrics and Gynaecology, “Sapienza” University of Rome, Italy

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/m² and paclitaxel 175 mg/m², 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
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:
- Overall survival [ Time Frame: 7 years ]
- Overall 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

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental: Cisplatin plus gemcitabine</td>
<td>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.</td>
</tr>
<tr>
<td>Experimental arm: NACT (cisplatin plus gemcitabine) followed by surgery</td>
<td></td>
</tr>
<tr>
<td>Control arm: concurrent chemoradiation (cisplatin/carboplatin) during standard radiation</td>
<td></td>
</tr>
</tbody>
</table>
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
Ib2–IVa were treated with neoadjuvant cisplatin 35 mg/m² and Gemciabine 1000 mg/m² D1 and D8, for 2 cycles. Then, they received CRT (50.4 Gy) with weekly Cisplatin 40 mg/m² 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 ]
Estimated Enrollment: 770
Study Start Date: September 2012
Estimated Study Completion Date: September 2021

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Comparator: Chemoradiation</td>
<td>- Radiation: Radiotherapy</td>
</tr>
<tr>
<td>Radiotherapy (external beam and brachytherapy) plus concurrent Cisplatin weekly for 5 weeks</td>
<td>- Radiation comprising external beam 40-50.4Gy in 20-28 fractions plus intracavity brachytherapy to achieve a minimum total EQD2 dose of 78-86Gy.</td>
</tr>
<tr>
<td>Drug: Cisplatin</td>
<td>- 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.</td>
</tr>
<tr>
<td>Experimental: Induction Chemotherapy + Chemoradiation 6 cycles of weekly Paclitaxel and Carboplatin followed by Chemoradiation as per Active Comparator</td>
<td>- Drug: Paclitaxel</td>
</tr>
<tr>
<td>Drug: Paclitaxel</td>
<td>- Paclitaxel 80 mg/m2 (capped at 160mg maximum total dose) weekly for 6 weeks i.e. on days 1, 8, 15, 22, 29 &amp; 36.</td>
</tr>
<tr>
<td>Drug: Carboplatin</td>
<td>- Carboplatin AUC 2 (capped at 270mg maximum total dose) weekly for 6 weeks i.e. on day 1, 8, 15, 22, 29, &amp; 36.</td>
</tr>
<tr>
<td></td>
<td>- Chemo Radiotherapy: Same protocol</td>
</tr>
</tbody>
</table>
CCT-RT

NACT ↓

surgery
Postoperative pelvic EBRT with concurrent cisplatin-containing chemotherapy (category 1)\textsuperscript{140} 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, parametrical extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy.\textsuperscript{140} 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 microsccous parametrical involvement.

Cancer in the NCCN Guidelines) with (or without) individualized EBRT.\textsuperscript{187}

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\textsuperscript{197-199} or locally-advanced cervical cancer.\textsuperscript{200,201} 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.\textsuperscript{201} However, data from a second meta-analysis suggested that response to neoadjuvant chemotherapy was a strong prognostic factor for PFS and overall survival.\textsuperscript{202,203} 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?
Stage IIB-IVA squamous cervical cancer
KPS >60%
Adequate organ function

Neoadjuvant CT (Cisplatin + Vincristine + Bleomycin) x3 followed by RT and intracavitary RT

Rural-based
Urban-based

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NACT Arm (Group A) (%)</td>
</tr>
<tr>
<td>II B</td>
<td>32/63 (50.8)</td>
</tr>
<tr>
<td>III A</td>
<td>17/21 (81)</td>
</tr>
<tr>
<td>III B</td>
<td>21/105 (20)</td>
</tr>
<tr>
<td>IV A</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>70 (35)</td>
</tr>
</tbody>
</table>

Table 5: Patterns of relapse in both arms

<table>
<thead>
<tr>
<th>Site of relapse</th>
<th>Group A (n=16)</th>
<th>Group B (n=27)</th>
<th>P value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>14 (87.5)</td>
<td>25 (94.4)</td>
<td>0.619</td>
<td>1.156</td>
</tr>
<tr>
<td></td>
<td>(63-2.094)</td>
<td>(63.7-2.094)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>2 (12.5)</td>
<td>2 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)
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