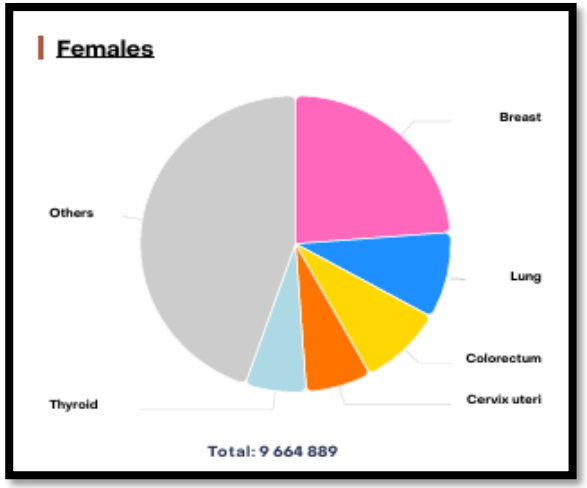
# Neoadjuvant And Adjuvant Trials In Carcinoma Cervix Interlace Trial And Beyond

**Dr Sweety Gupta**
Additional Professor
Department of Radiation Oncology
AIIMS Rishikesh

# Incidence

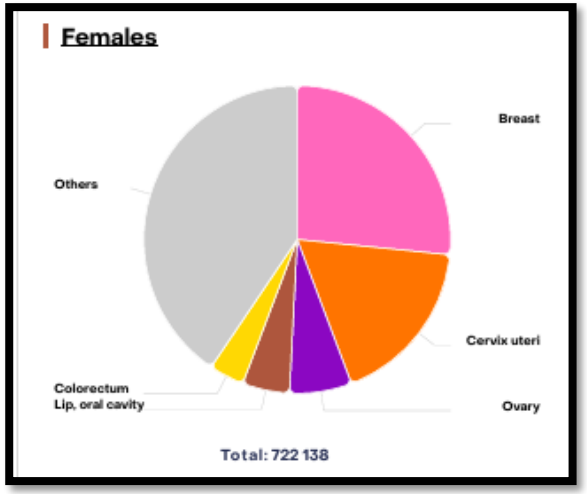
Cervical cancer 4th MC cancer among women globally

- 662,301 new cases and 348 874 deaths in 2022

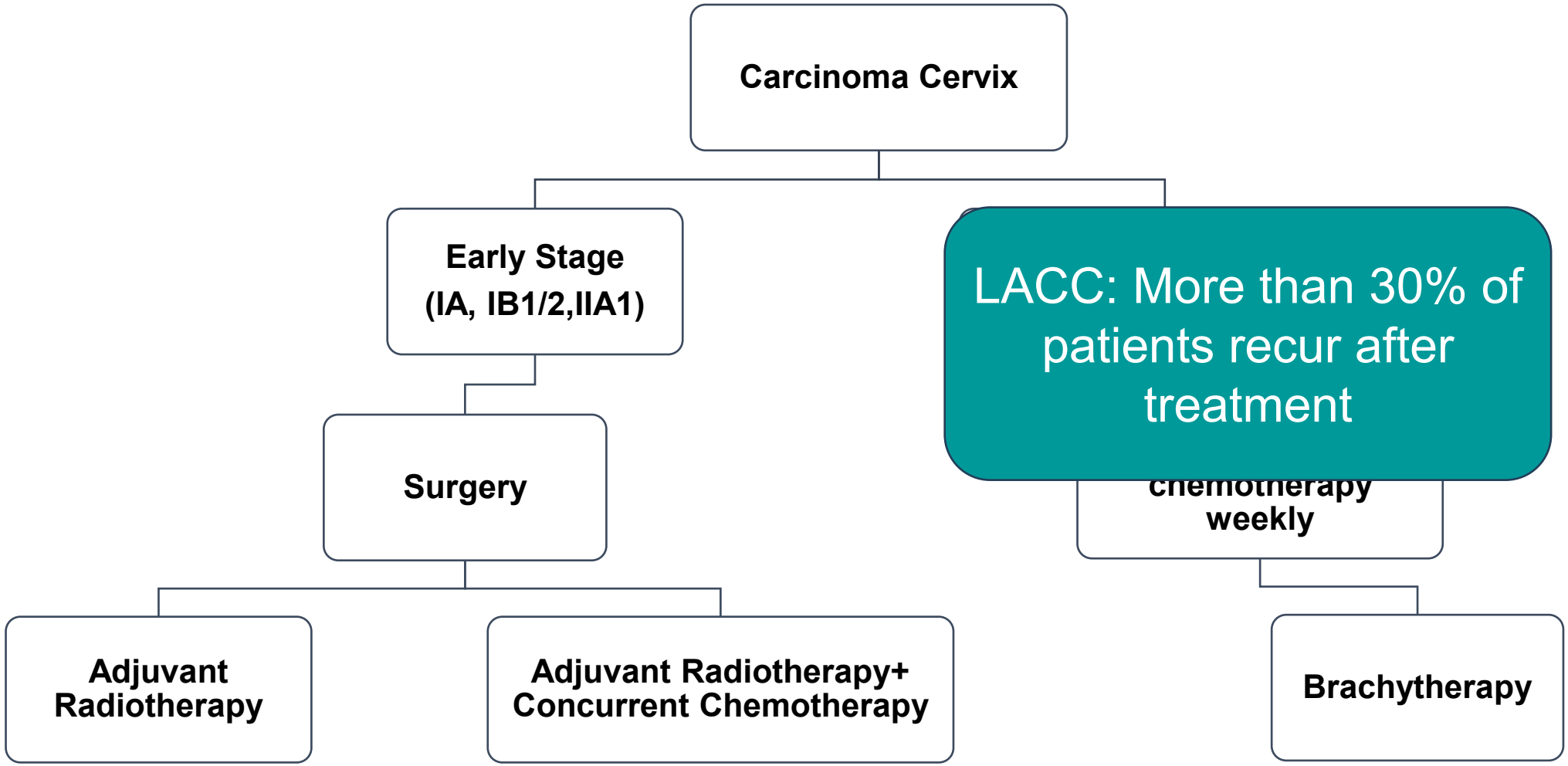



In India, 2nd MC cancer among women

- 1,27,526 new cases and 79,906 deaths annually



# Carcinoma Cervix Management



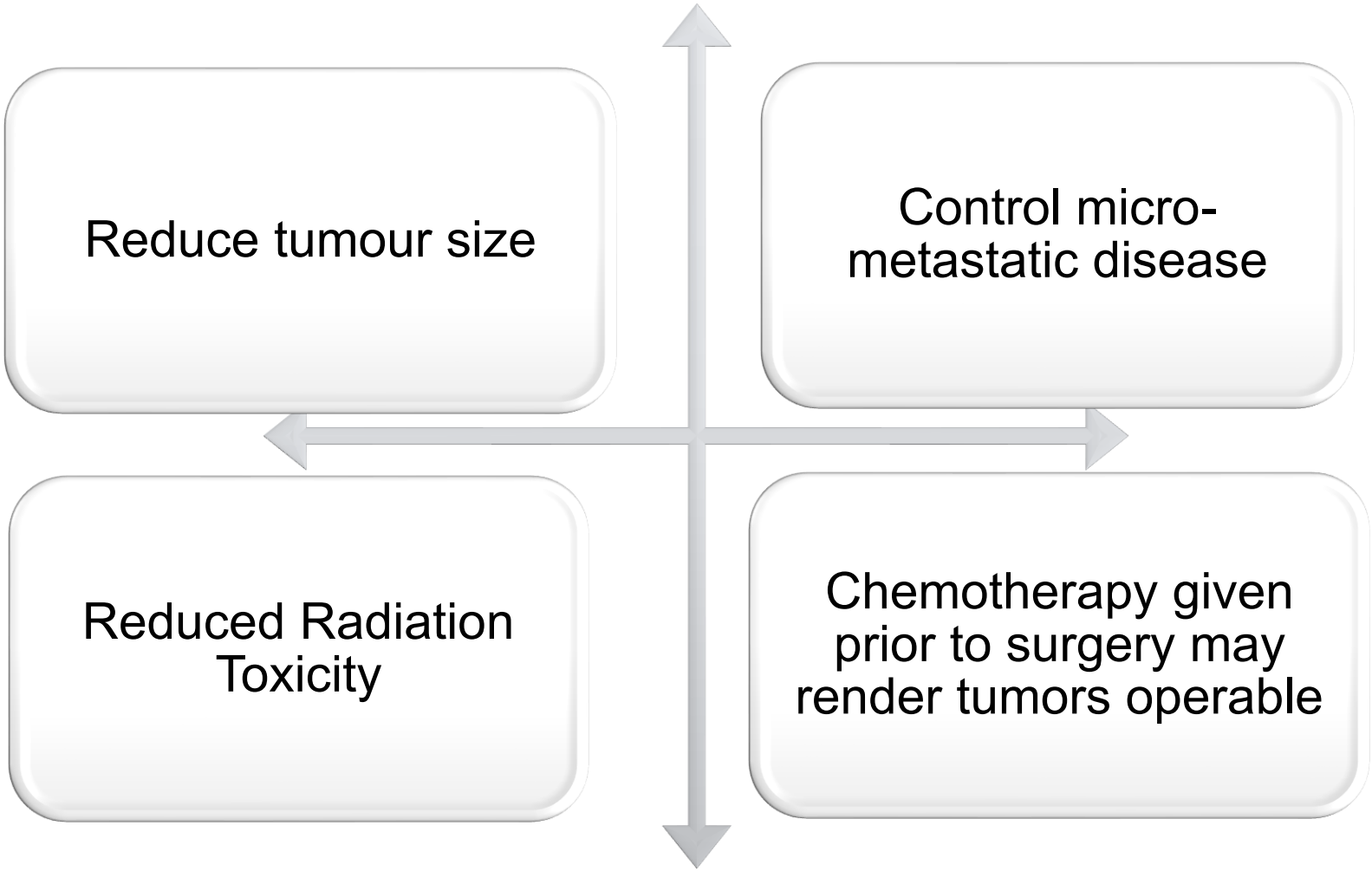
# Survival

| Stage | 5-Year Survival Rate |
|---|---|
| I | 85.6% |
| • IA | 94.1% |
| IB | 75.9% |
| • IB1 | 91.6% |
| • IB2 | 83.3% |
| • IB3 | 76.1% |
| II | 56.1% |
| • IIA | 63.4% |
| • IIB | 62.9% |
| III | 39.3 % |
| • IIIA | 40.7% |
| • IIIB | 41.4% |
| • IIIC | 46.3 % |
| • IIIC1 | 60.8% |
| • IIIC2 | 37.5% |
| IVA | 24.0% |
| IVB | 14.7% |

Wright, Jason D. et al Prognostic Performance of the 2018 International Federation of Gynecology and Obstetrics Cervical Cancer Staging Guidelines. Obstetrics & Gynecology 2019.


Neoadjuvant Chemotherapy
Surgery
Radiotherapy
Adjuvant Chemotherapy

# Rationale for Neoadjuvant Chemotherapy



# Neoadjuvant chemotherapy plus surgery versus surgery

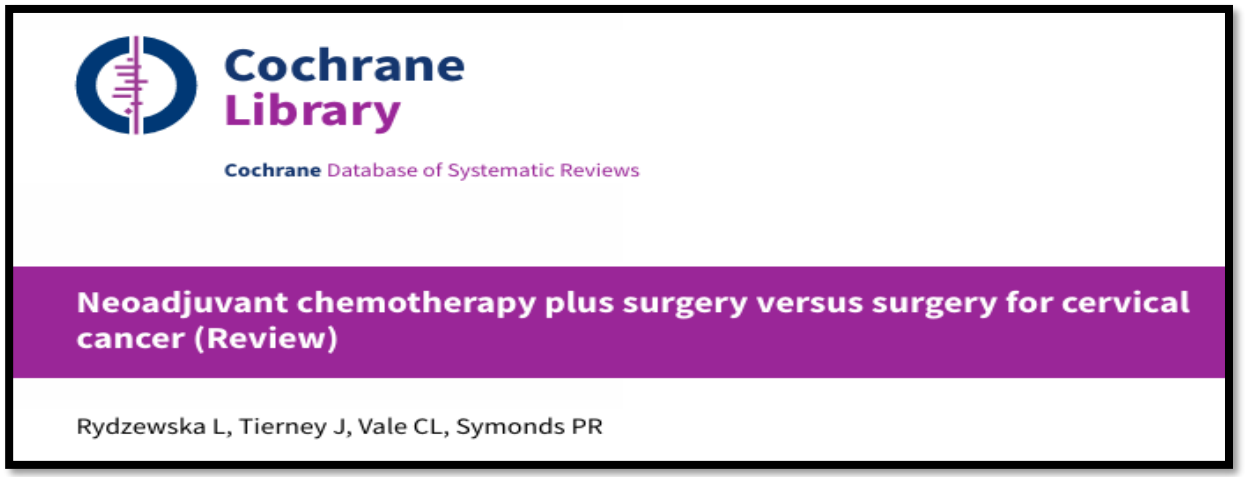
# NACT followed by Surgery vs Surgery

NACT: potential for reducing tumour volume, increasing resectability and control micrometastatic disease

6 RCTs; N-1078

Stage: IB2-IIB

NACT ⟶ Radical Surgery versus Radical Surgery




- **OS (p=0.02)** and **PFS (p=0.008)** significantly improved with NACT
- Distant recurrence and resection rates were not significantly improved but trended in favour of NACT
- Pathological response was significantly better with NACT:
  - Lymph node positivity: OR 0.5
  - Parametrial infiltration: OR 0.58

**Limitations**

- **Heterogeneity in chemo regimens**
- **NACT arm: post-op RT in 45% pts**
- **In Surgery arm: post-op RT in 52% pts**

**Rydzewska L, et al Cochrane Database Syst Rev 12: CD007406, 2012**

# Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concurrent Chemoradiation

# NACT → Surgery vs CCRT

| Authors | 872; 5 trials Cochrane (NACCCMA 2004) | 633 (Gupta et al., 2018, JCO) | 626 EORTC 55994 Trial (Ramirez et al., 2019, JCO) |
|---|---|---|---|
| **Design** | Meta analysis | Phase III RCT, single-country | Phase III RCT, multi-centric |
| **Population** | IB-IIIB | Stage IB2, IIA, IIB ( SCC) | Stage IB2–IIB (all histologies included) |
| **Inter** | | | ne+ |
| **Cont** | | | |
| **Prim** | | | |
| **Path resp** | | | |
| **Addi Treatment** | 30-98 % Adjuvant RT | 25 % Adjuvant RT, NA | 46 % adjuvant RT, 8 % Surgery |
| **Results – DFS** | **p=0.02** | NACT+Surgery: 69.3% CCRT: 76.7% (**p = 0.038**) | 57% vs 66% **(p=0.011)** |
| **Results – OS** | **p = 0.006** | NACT+Surgery: 75.4% CCRT: 84.8% (**p = 0.041**) | 72% vs 76% |
| **Conclusions** | NACT+Surgery superior in both DFS and OS | CCRT was superior to NACT+Surgery in both DFS and OS | NACT+Surgery was **non-inferior** to CCRT for DFS |

- **Stage heterogeneity**
- **NACT regimen varied**
- **Observed benefits may be attributable in part to adjuvant radiotherapy rather than NACT alone**

# Neoadjuvant Chemotherapy followed by Radiotherapy Vs Radiotherapy

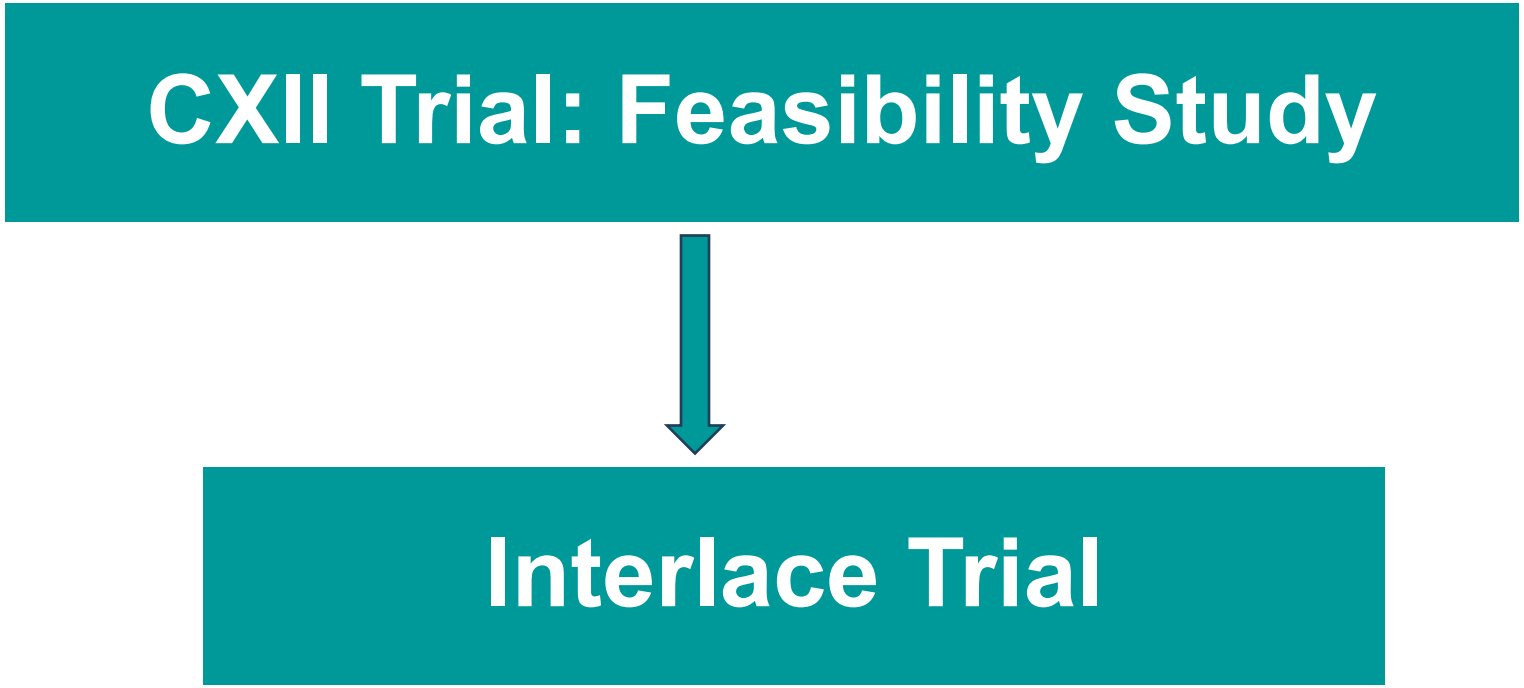
# NACT ⟶ Radiotherapy vs CCRT

| Study | Stage | NACT regimen | RT | Median FU (mo) | Key outcomes | Toxicity |
|---|---|---|---|---|---|---|
| **Cochrane NACCC 18 tria** | | CIS/BLM/5FU/Taxane/MT | | | **5 years OS:** | -- |
| **Narayan Retrospe** | | | | | | ade 3/4 atologic: in NACT vs (p=0.001) |
| **da Costa et al. RCT Phase II 2019; 107** | IIB–IVA | Cis 50 mg/m² d1 + **Gem 1000 mg/m²** d1,8 q3w ×3 | EBRT 45–50.4 Gy/25–28# BT 7–7.5 Gy ×4 | 31.7 | (p=0.008)<br>3-yr PFS: 40.9% vs 60.4%<br>**3-yr OS: 60.7% vs 86.8% (p=0.007)** | Neuropathy: 25.4% vs 1.9% (p=0.002) |
| **Fenghu Li et al. RCT 2024; 146** | IB2–IVA | Pacli 135–175 mg/m² + Cis 60–80 mg/m² q3w ×2 | EBRT 50.4 Gy/28# (56.4–60.2 Gy to nodes);<br>BT 6 Gy ×5 | 21 | CR at 1 yr: 87.7% vs 67.6% (p=0.000); **OS/PFS NS**<br>Failures: 11% vs 17.6% (p=0.021) | Thrombocytopenia in NACT (16.4% vs 13.2%; p=0.045) |

- **NACT 3 weekly used; Gemcitabine toxicity high**
- **Shorter chemotherapy cycles (<14 days) and Higher cisplatin dose intensity (>25mg/m²/week) were associated with benefit**
-

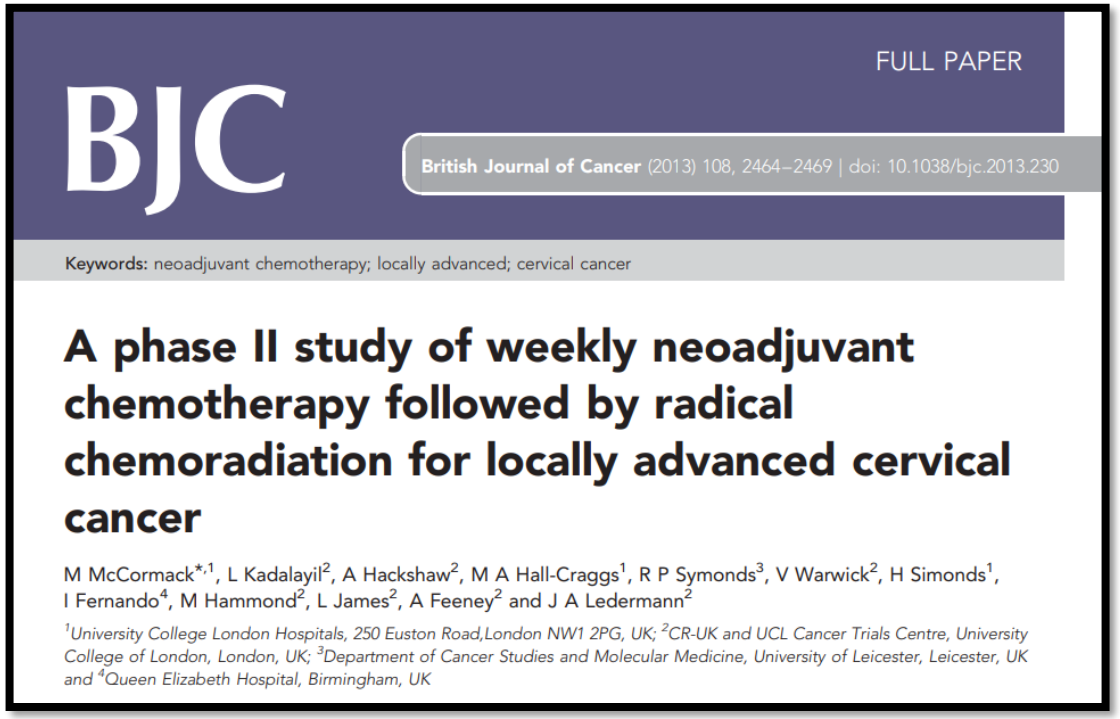
# Issues with these trials

- Dose intensity and cycle interval (e.g., ≤14 days) were key factors influencing outcomes
- Chemotherapy drugs varied considerably
- Inconsistent overall survival benefit
- High study heterogeneity


CXII Trial: Feasibility Study
Interlace Trial

# CXII Trial: Feasibility Study

- N=46
- FIGO stage Ib2-IVa
- Histologically positive para-aortic lymph nodes
- NACT : weekly paclitaxel (80 mg m 2 ); carboplatin (AUC 2)
- EBRT: Pelvis 50.4 Gy / 28 fr + Cisplatin 40 mg m 2; PAN: 45Gy/25fr
- Brachytherapy: 15 Gy / 2fr
- **Primary end point**: response at 12 weeks post RT



FULL PAPER

BJC

British Journal of Cancer (2013) 108, 2464–2469 | doi: 10.1038/bjc.2013.230

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*[,1], L Kadalayil[2], A Hackshaw[2], M A Hall-Craggs[1], R P Symonds[3], V Warwick[2], H Simonds[1], I Fernando[4], M Hammond[2], L James[2], A Feeney[2] and J A Ledermann[2]

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

**McCormack M, et al A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. Br J Cancer. 2013 Jun 25;108(12):2464-9.**

# Results

**Compliance**

- 80% completed 6 NACT cycles
- 98% completed radiotherapy
- 78% received ≥4 cycles of cisplatin during CRT

**To**

- NACT: 20% (11% hematologic, 9% non-hematologic)

g (9%)

Weekly dose-dense NACT with carboplatin/paclitaxel followed by CRT is

**feasible**, **tolerable**, and demonstrates a **high response rate**

**Survival**

- 3/5year OS: 67%
- 3-year PFS: 68%

Active, not recruiting

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

**ClinicalTrials.gov ID** NCT01566240

**Sponsor** University College, London

**Information provided by** University College, London (Responsible Party)

**Last Update Posted** 2024-12-05

# Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally advanced cervical cancer (GCIG INTERLACE): an international, multicentre, randomised phase 3 trial

*Mary McCormack, Gemma Eminowicz, Dolores Gallardo, Patricia Diez, Laura Farrelly, Christopher Kent, Emma Hudson, Miguel Panades, Tony Mathew, Anjana Anand, Mojca Persic, Jennifer Forrest, Rajanee Bhana, Nicholas Reed, Anne Drake, Madhavi Adusumalli, Asima Mukhopadhyay, Margaret King, Karen Whitmarsh, John McGrane, Nicoletta Colombo, Choi Mak, Ranajit Mandal, Rahul Roy Chowdhury, Gabriela Alamilla-Garcia, Adriana Chávez-Blanco, Hilary Stobart, Amanda Feeney, Simran Vaja, Anne-Marie Hacker, Allan Hackshaw, Jonathan Andrew Ledermann, on behalf of the INTERLACE investigators**

McCormack M, et al. INTERLACE investigators. (GCIG INTERLACE): an international, multicentre, randomised phase 3 trial. Lancet. 2024 Oct 19;404(10462):1525-1535

# Methodology

## Study Design

- Multicentric , Randomized phase 3 trial; open label; 32 medical centres

## Randomization

- 1:1

## Allocation

- Central  electronic system

## Stratification  factors

- Recruiting site
- FIGO stage
- Positive or negative nodal status
- Three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiation therapy (IMRT)
- Age
- Tumour size
- Squamous or non-squamous histology

# Selection Criteria

N= 500

Adults (aged ≥18 years) with newly diagnosed histologically confirmed locally advanced cervical cancer

**Inclusion Criteria**

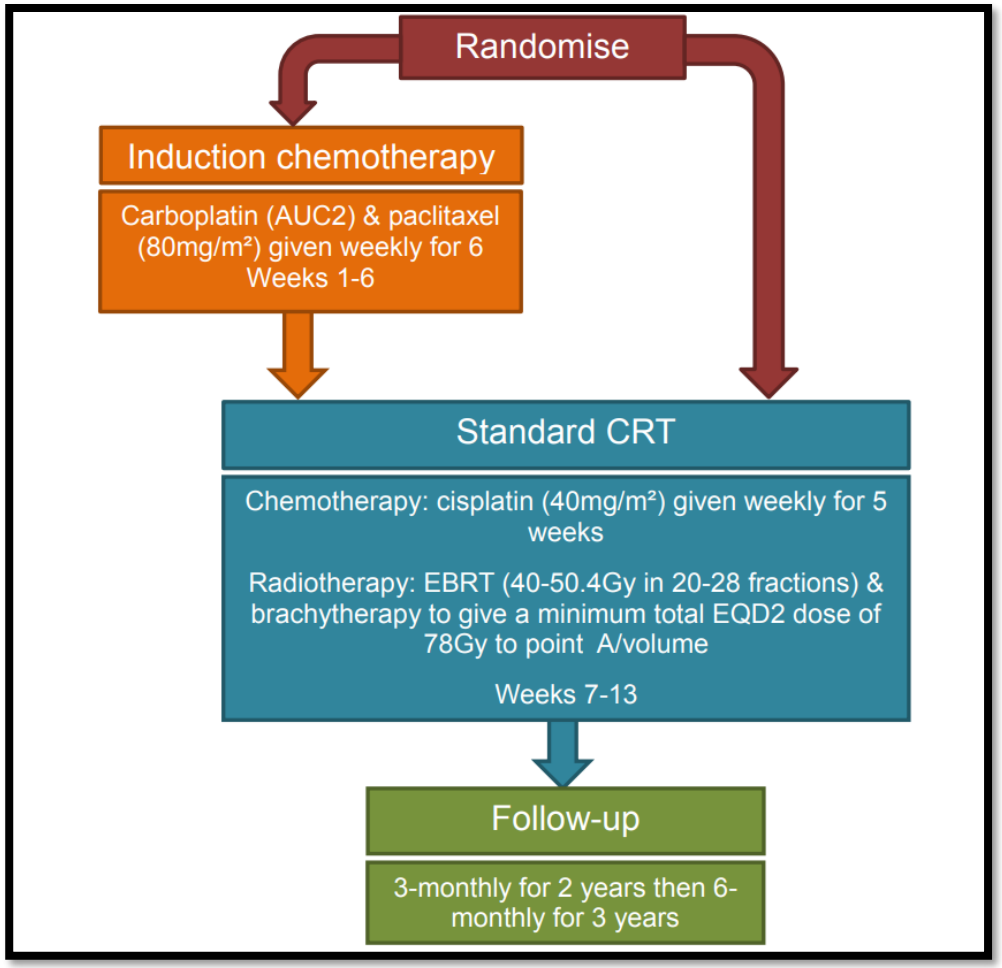
- Stage IB1 disease with nodal involvement, IB2, IIA, IIB, IIIB, or IVA
- Squamous, adenocarcinoma,or adenosquamous histology
- Fit for radical treatment
- No positive lymph nodes above the aortic bifurcation
- Positive lymph nodes: histologically positive or PET-positive, or at least 15 mm on CT or MRI

**Exclusion Criteria**

- FIGO 2008 stage IIIA disease
- Presence of para-aortic nodes
- Distant metastases
- Previous pelvic malignancy

# Procedure

- Baseline  imaging (CT chest or abdomen or PET-CT, MRI, or CT pelvis)
- Physical examination: once a week during chemoradiotherapy and induction chemotherapy
- Clinical examination
  - Week  4 and 12 after treatment completion
  - Once  every 3 months for years 1 and 2
  - Once  every 6 months for years 3, 4, and 5




Quality of life (QoL) assessments:

- Baseline , weeks 1 and 3 of chemoradiotherapy, then at clinical reviews thereafter
- Induction chemotherapy patients had an additional QoL assessment at week 4 of induction chemotherapy

# Outcomes

**Primary endpoints**

- Overall survival
- Progression-free survival

**Secondary endpoints**

- Adverse events
- Pattern of first relapse
- Time to next anticancer therapy
- Health-related QoL (QLQ-C30 and QLQ-CX24)

# Results

- N=500 pts ; 32 Centres
- Median age 46 (range 24–78) years
- PET CT Scan: 25% of patients

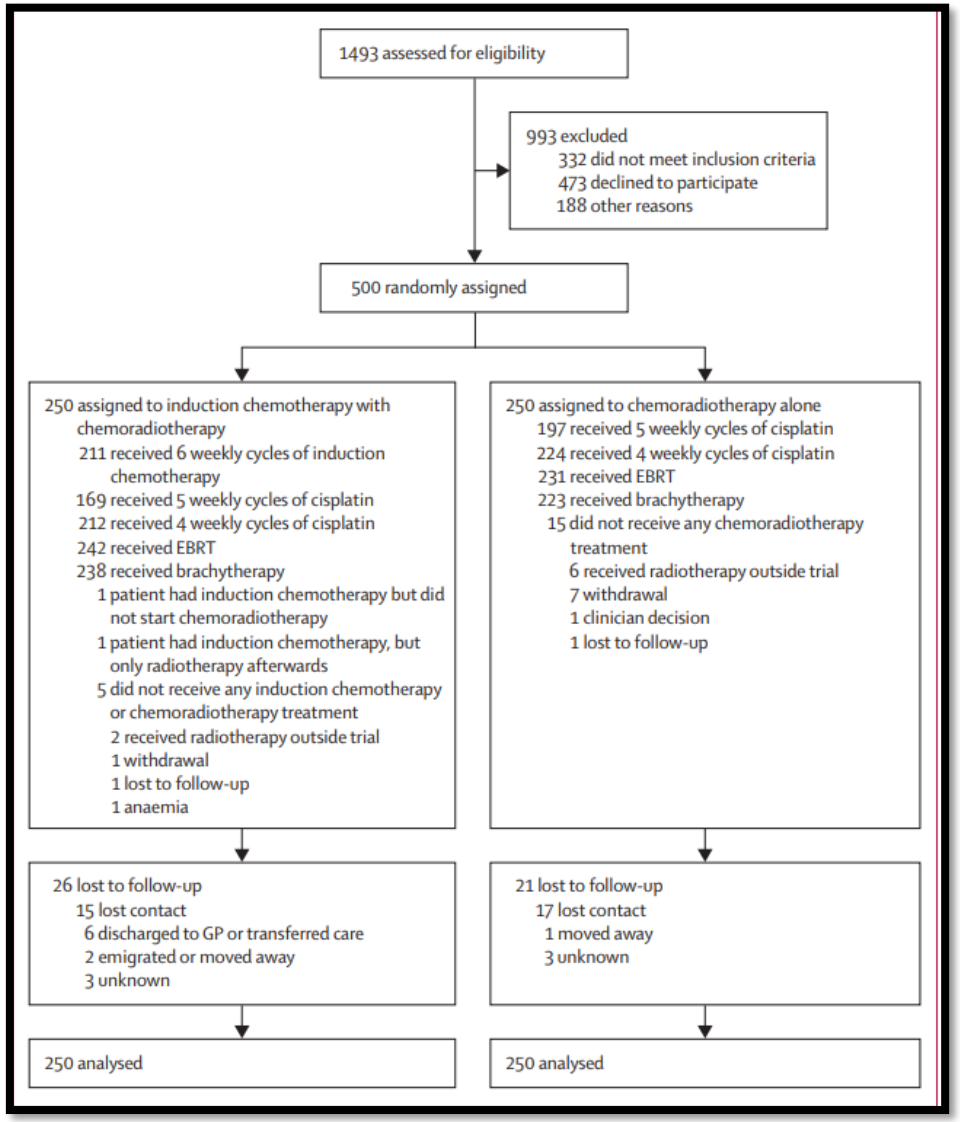



**Figure 1: Trial profile**

# Results

| | Induction chemotherapy with chemoradiotherapy (n=250) | Chemoradiotherapy alone (n=250) |
|---|---|---|
| Age, years* | 46 (26–78) | 46 (24–78) |
| ECOG status | | |
| 0 | 214 (86%) | 221 (88%) |
| 1 | 36 (14%) | 29 (12%) |
| Country | | |
| UK | 190 (76%) | 190 (76%) |
| Mexico | 49 (20%) | 51 (20%) |
| Italy | 5 (2%) | 3 (1%) |
| India | 5 (2%) | 5 (2%) |
| Brazil | 1 (<1%) | 1 (<1%) |
| FIGO stage (2008) | | |
| IB1 | 2 (1%) | 2 (1%) |
| IB2 | 19 (8%) | 23 (9%) |
| IIA | 17 (7%) | 14 (6%) |
| IIB | 178 (71%) | 176 (70%) |
| IIIB | 26 (10%) | 30 (12%) |
| IVA | 8 (3%) | 5 (2%) |
| Cell stage | | |
| Non-squamous | 44 (18%) | 45 (18%) |
| Squamous | 206 (82%) | 205 (82%) |
| Nodal status | | |
| Negative | 144 (58%) | 141 (56%) |
| Positive | 106 (42%) | 109 (44%) |
| FIGO stage (2018) | | |
| I and II | 128 (51%) | 126 (50%) |
| IIIB and IVA | 22 (9%) | 16 (6%) |
| IIIC | 100 (40%) | 108 (43%) |
| Longest tumour diameter, cm† | 4·8 (1·3–13·5) | 4·9 (1·8–12·8) |

**Table 2: Baseline characteristics**

| | Induction chemotherapy (n=250) |
|---|---|
| Paclitaxel with carboplatin cycles completed | |
| Six cycles | 211 (84%) |
| At least five cycles | 230 (92%) |
| Main reasons for fewer than six cycles | |
| Adverse events | 29 (12%) |
| Haematological | 9 |
| Non-haematological | 17 |
| Both | 3 |
| Withdrawal or other reasons not due to toxicity | 10 (4%) |
| Median interval from induction chemotherapy to radiotherapy, days | 7 (5–54) |

**Induction chemotherapy Adherence in patients**

# Results

3D CRT: 58 and 60% respectively

Overall radiation treatment time **exceeded** > 56 days

Induction Chemo: nine (4%) / 242 patients

ChemoRT: seven (3%) / 231 patients

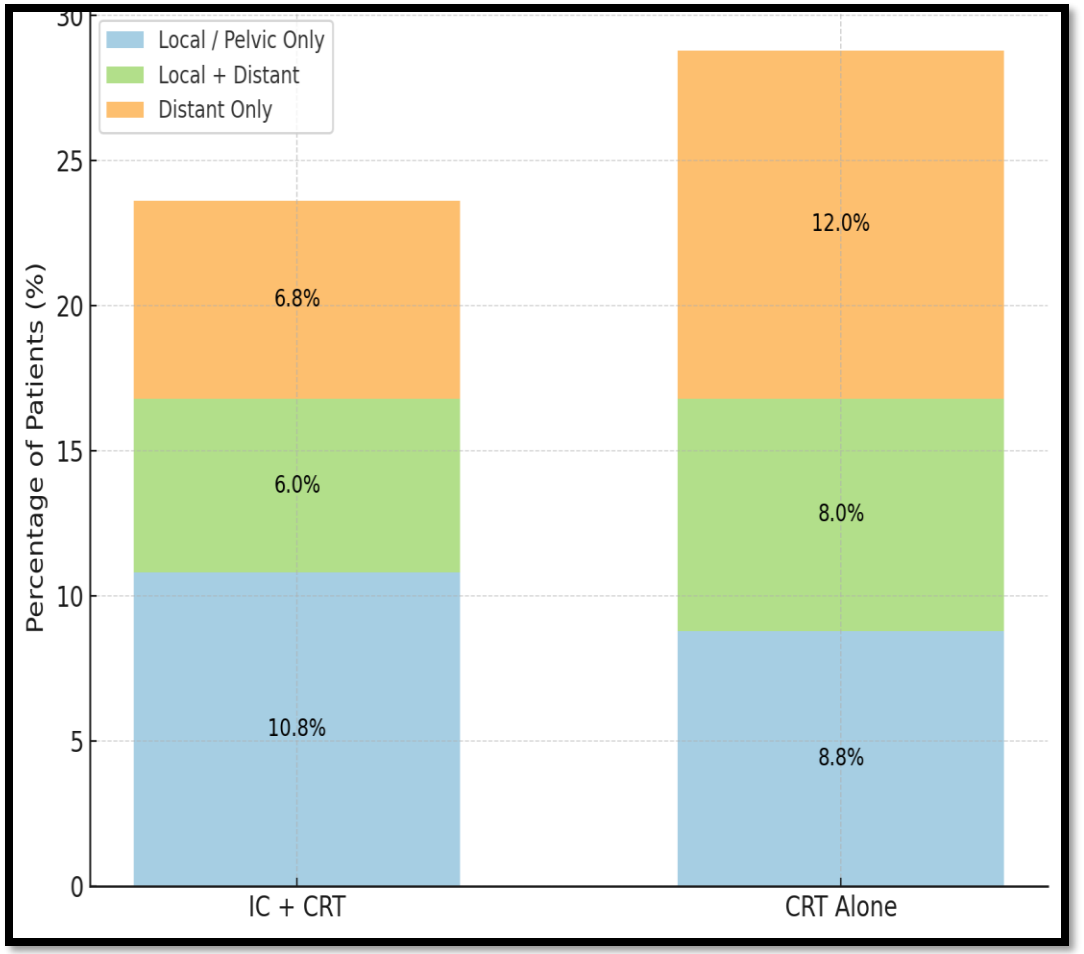
Main reasons

- Radiotherapy and brachytherapy scheduling problems (9) and adverse events (5)

| | Induction chemotherapy with chemoradiotherapy (n=250) | Chemoradiotherapy alone (n=250) |
|---|---|---|
| **Cisplatin cycles completed** | | |
| Five cycles | 169 (68%) | 197 (79%) |
| At least four cycles* | 212 (85%) | 224 (90%) |
| Main reasons for fewer than five cycles | | |
| Adverse events leading to discontinuation | 68 (27%) | 33 (13%) |
| Haematological | 34 | 4 |
| Non-haematological | 20 | 25 |
| Both | 14 | 4 |
| Other reasons not due to toxicity | 13 (5%) | 20 (8%) |
| **Radiotherapy** | | |
| Received definitive EBRT on or off trial† | 246 (98%) | 239 (96%) |
| Received EBRT on trial | 242 (97%) | 231 (92%) |
| IMRT | 102 (42%) | 93 (40%) |
| 3DCRT | 140 (58%) | 138 (60%) |
| Received extended field EBRT | 22 (9%) | 20 (9%) |
| Received brachytherapy | 238 (98%) | 224 (97%) |
| 2D point A | 46 (19%) | 49 (22%) |
| 3D point A | 120 (50%) | 107 (48%) |
| 3D HRCTV D90 | 72 (30%) | 68 (30%) |
| Did not receive brachytherapy on trial | 4 (2%) | 7 (3·0%) |
| Received EBRT boost | 3 (1%) | 6 (2·6%) |
| No boost | 1 (<1%) | 1 (<1%) |
| Did not receive EBRT on trial | 8 (3%) | 19 (8%) |
| Had radiotherapy outside trial | 4 (50%) | 8 (42%) |
| Ineligible or discontinued | 1 (13%) | 5 (26%) |
| No EBRT | 1 (13%) | 1 (5%) |
| Unknown | 2 (25%) | 5 (26%) |
| Median overall treatment time, days | 45 (36–70) | 45 (37–88) |
| Median total EQD2, Gy (% ≥78 Gy)‡ | 79·4 (69·8) | 80·0 (71·4) |
| Median total HRCTV D90 EQD2 (IGABT), Gy‡ | 86·6 | 86·8 |

# Results: Relapse

- **Distant-only relapses** were notably fewer in the IC + CRT group
- **Local and combined relapses** were relatively comparable
- **Para-aortic recurrence** was rare in both arms 1 and 3

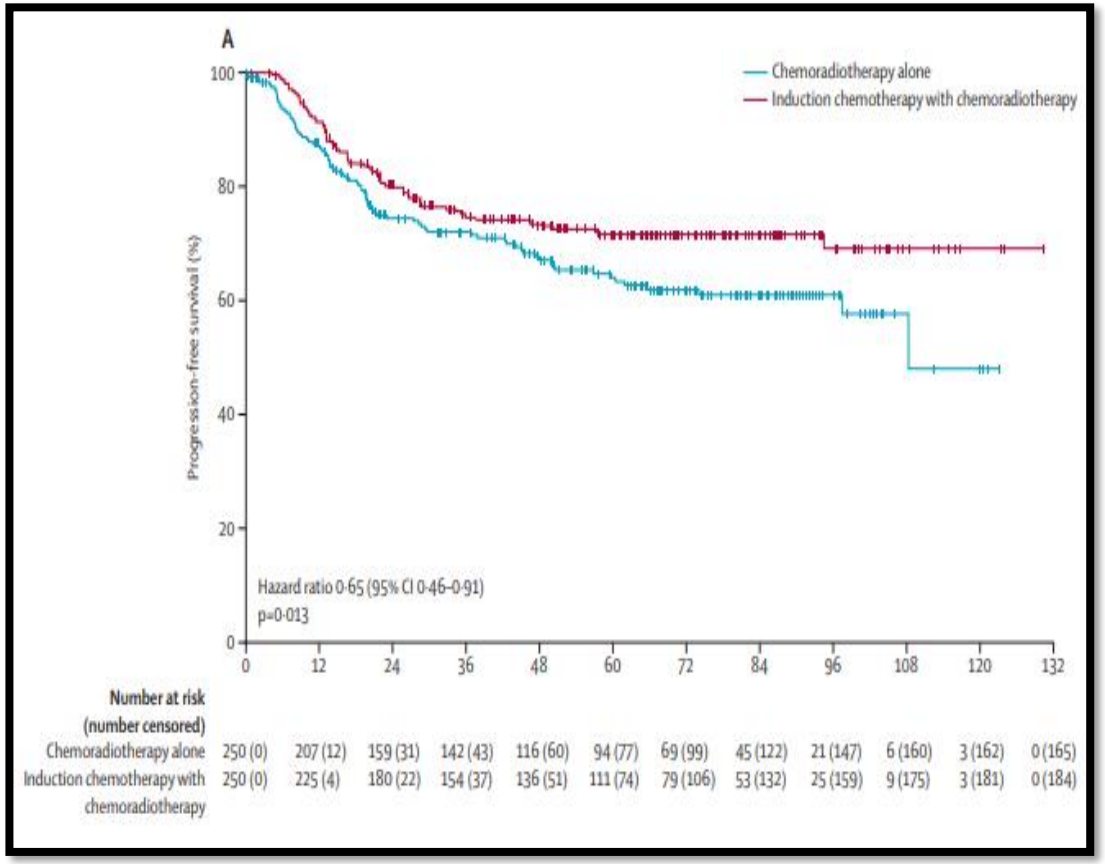


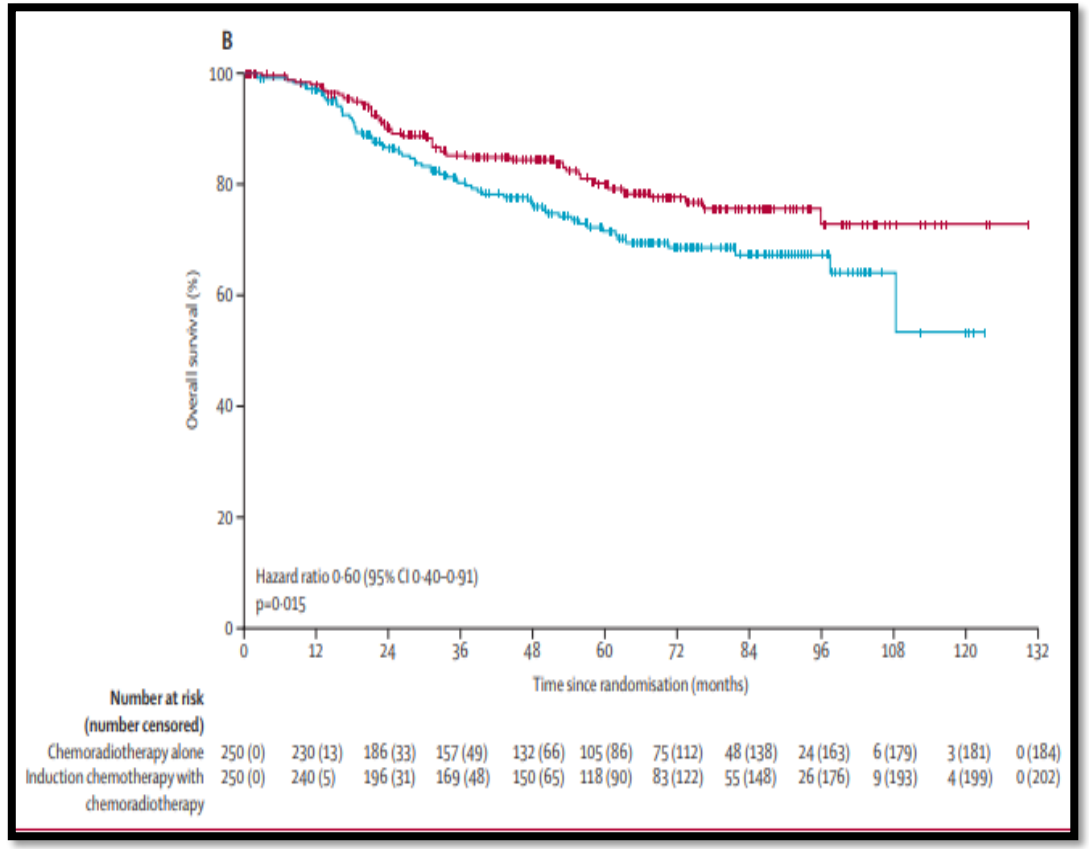

**Patterns of Relapse in INTERLACE Trial**

# Results: Survival

| Parameter | IC + CRT Arm (n=250) | CRT Alone Arm (n=250) | P-value / HR / Notes |
|---|---|---|---|
| 5-year Progression-Free Survival (PFS) | 72% | 64% | HR 0.65 (95% CI 0.46–0.91); p=0.013 |
| 5-year Overall Survival (OS) | 80% | 72% | HR 0.60 (95% CI 0.40–0.91); p=0.015 |
| 3-year PFS | 75% | 72% | Absolute diff: 2.8–8.7% |
| 3-year OS | 85% | 80% | Absolute diff: 5% |
| Distant-only relapse rate | 7% | 12% | p=0.015 |
| Local/pelvic relapse | 11% | 9% | Not significant |
| Grade ≥3 Adverse Events (any) | 59% | 48% | More hematologic AEs in IC group |
| ▸ Grade ≥3 Neutropenia | 19% | 5% | Mostly during induction phase |
| ▸ Grade ≥2 Anaemia | 28% | 17% | Higher in IC arm |
| ▸ Grade ≥3 Diarrhea | 8% | 12% | Lower in IC arm |
| Cisplatin ≥5 cycles | 68% | 79% | Slightly fewer in IC group |
| Cisplatin ≥4 cycles | 85% | 90% | Acceptable in both |
| Median Treatment Duration (Radiotherapy) | 45 days | 45 days | Similar |
| Received EBRT + Brachytherapy | 238 (98%) | 224 (97%) | Comparable |
| Deaths within 30 days of treatment | 1 (0.4%) | 2 (0.8%) | None treatment-related |

# Results: KM Graph PFS /OS




Kaplan–Meier estimates of progression-free survival (A) and overall survival (B)

# Results: Causes of death

| Cause of Death | IC + CRT (N=250) | CRT Alone (N=250) | Number (%) |
|---|---|---|---|
| **Disease progression** | 42 | 52 | 16.8% vs 20.8% |
| **Non–treatment-related** | 6 | 12 | 2.4% vs 4.8% |
| **Unknown** | 0 | 2 | 0% vs 0.8% |
| **Total deaths** | 48 | 66 | 19.2% vs 26.4% |

Fewer deaths occurred in the IC + CRT arm

Most deaths were due to disease progression in both arms

Non-treatment-related deaths were slightly more frequent in the CRT alone arm.

# Interlace Trial: Conclusion

| | |
|---|---|
| **Improved Survival** | • Induction chemo + CRT improved 5-year PFS (72% vs 64%) and OS (80% vs 72%) |
| **Better Distant Control** | • Reduced distant-only relapses (7% vs 12%) |
| **Manageable Toxicity** | • Higher Grade 3–4 toxicities, mainly neutropenia, but no rise in infections or deaths |
| **Feasible Protocol** | • High treatment compliance; median 7-day gap between chemo and CRT |
| **Practice-Changing** | • New standard of care for locally advanced cervical cancer<br>• Resource limitations and long radiotherapy waiting times?? |
| **Foundation for Future Trials** | • Sets platform for combining with immunotherapy or novel agents |

# Limitations

**Toxicity**

- **Higher rates of Grade 3–4 adverse events (59% vs 48%),** particularly hematologic (neutropenia)
  - Despite not translating to higher infection-related mortality, it may pose challenges in settings lacking supportive care

**Generalizability**

- **Only 14% had FIGO IIIB–IVA,** and patients with para-aortic nodes were excluded
  - Applicability to higher-risk subgroups is uncertain

**Radiotherapy Variation**

- **40 Gy also allowed**
  - Lower dose could compromise treatment of bulky tumors and microscopic nodal disease
- **Nodal status: ~43% had pelvic nodal involvement**
  - No mention of SIB (Simultaneous Integrated Boost) or boost EBRT doses to involved nodes
- **Only ~70% of patients received EQD2 ≥78 Gy**

**Delayed CRT Start in IC Arm**

- **Upto 22% had >7 days delay**

# Adjuvant Chemotherapy in Carcinoma Cervix

# Rationale of Adjuvant Chemotherapy

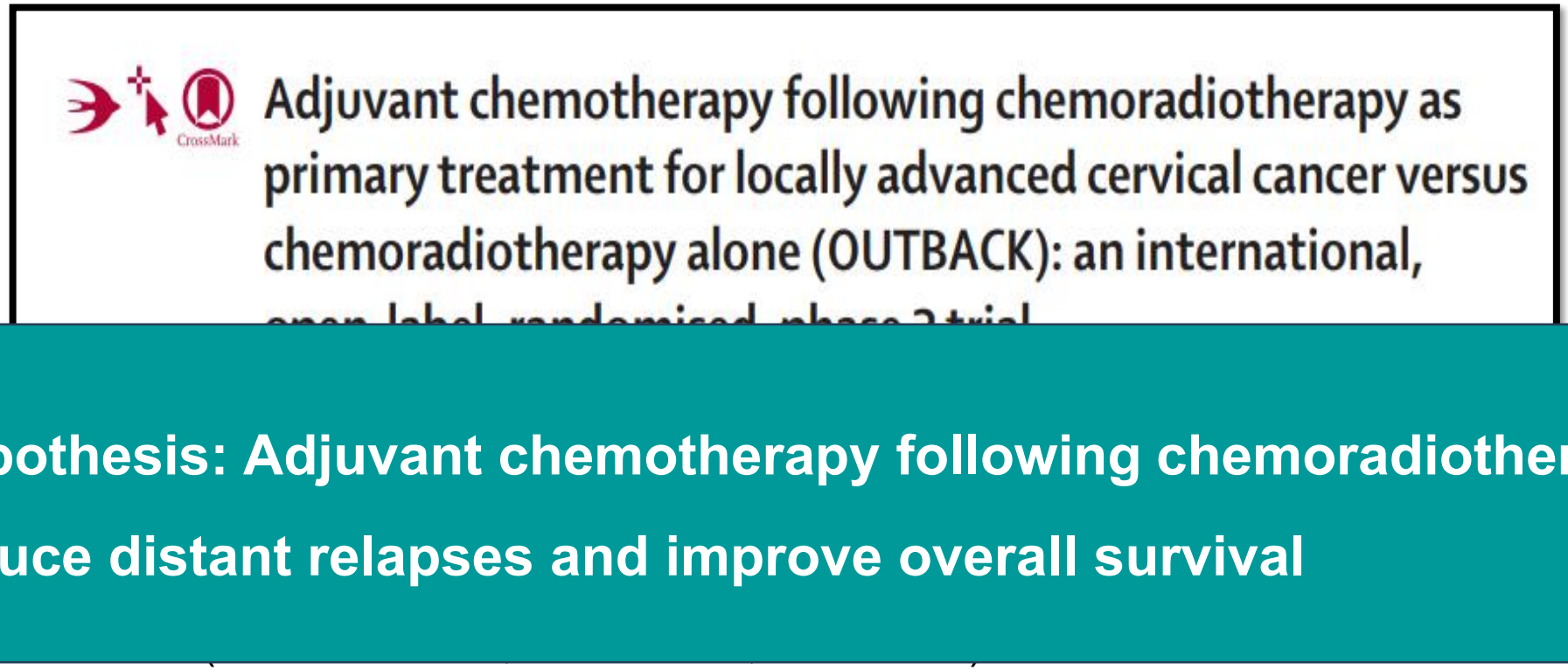
Improve survival by eradicating residual disease in the pelvis

Treating occult disease outside pelvis

# Adjuvant Chemotherapy in LACC

| Study | Design | Population | Intervention | Comparator | Primary Outcome | Drawbacks |
|---|---|---|---|---|---|---|
| **ACTLACC (2019)** | RCT (n=259) | Stage IIB–IVA | CCRT + 3 cycles paclitaxel/carboplati | CCRT alone | OS/PFS: No significant difference; ↓ systemic | **No OS benefit**; higher hematological toxicity |
| **Duel e** | | | | | | de ys |
| **Cochrane Review (2014)** | Systematic Review of 2 RCTs | Stage IIB–IVA | CCRT + ACT (varied drugs) | CCRT alone | Mixed: One trial OS benefit; other no benefit | Small number of trials; **heterogeneity;** risk of bias |
| **Asano et al. (2016)** | Narrative Review of retrospective studies | Early-stage (IA2–IIB) | Surgery + adjuvant chemotherapy alone | Surgery + RT/CCRT | Similar recurrence/OS; fewer complications vs RT/CCRT | No prospective RCTs; current evidence **retrospective** only |
| **Horeweg et al. Meta-analysis (2022)** | Systematic Review & Meta-analysis (8 studies, n=2150) | Stage IB2–IVA | CCRT + ACT (varied regimens) | CCRT alone | No significant OS/PFS benefit overall | Publication bias; **high toxicity**; not practice-changing |

**Adjuvant chemotherapy after CCRT in locally advanced cervical cancer shows no consistent survival advantage**




**Hypothesis: Adjuvant chemotherapy following chemoradiotherapy would reduce distant relapses and improve overall survival**

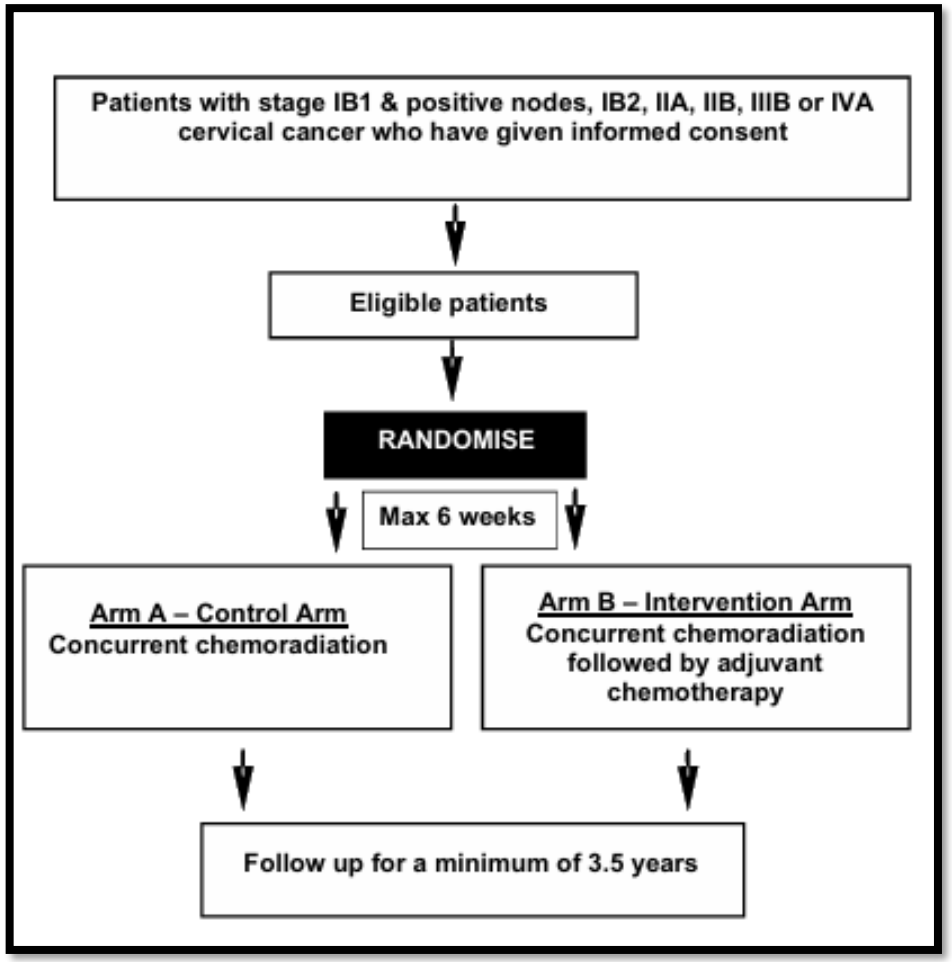
- Multicentre , open-label, randomised, phase 3 trial
- 157 hospitals

**Mileshkin LR, et al Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial. Lancet Oncol. 2023 May;24(5):468-482**

# Study Protocol

- EBRT: 45·0–50·4 Gy
- Participants with common iliac nodal disease received 45 Gy in 1·8 Gy fractions of extended field radiotherapy
- Parametrial or nodal boost was allowed at the discretion of the treating radio oncologist
- Cisplatin was given concurrently weekly 40 mg/m²
- HDR/LDR: total dose 80·0–86·4 Gy

After 4 weeks Adjuvant chemotherapy: carboplatin (AUC 5), paclitaxel (155 mg/m², intravenously over 3 h) q 21 days x 4 cycles




**IMRT was not allowed**

# Methodology

## Inclusion Criteria

- Histologically confirmed squamous cell carcinoma adenosquamous /adenocarcinoma of the cervix
- Stage IB1 disease with nodal involvement, or stage IB2, IIA, IIB, IIIB, or IVA disease)
- Eastern Cooperative Oncology Group performance status of 0–2
- Adequate bone marrow and organ function

## Exclusion Criteria

- Previous hysterectomy
- Para-aortic nodal involvement above the level of the common iliac nodes or above L3 or L4
- FIGO stage IIIA disease
- Disease assessed at presentation as requiring interstitial brachytherapy

# Outcomes

## Primary endpoint

- Overall survival rate at 5 years

## Secondary endpoints

- Progression -free survival rate at 3 and 5 years
- Acute and long-term toxicities
- Patterns of disease recurrence
- Radiation protocol compliance
- Patient self-reported quality of life

## Tertiary endpoint

- Metabolic response on a PET scan performed 4 – 6 months after treatment

# Results

- April 15, 2011 - June 26, 2017
- 926 participants
  - 456: Chemoradiotherapy only group
  - 463: Adjuvant chemotherapy group

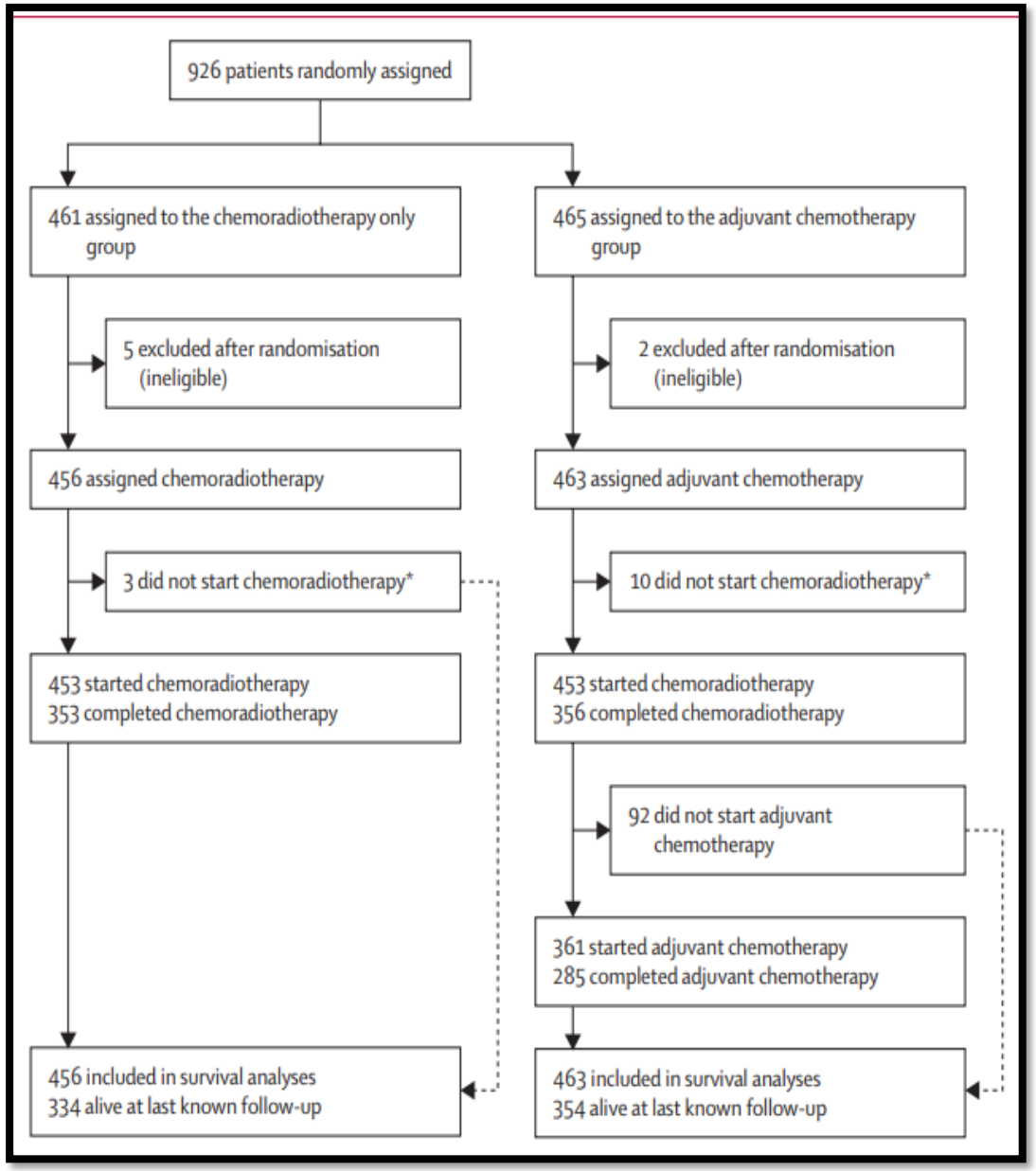



**Figure 1: Trial profile**

# Results: Patient Characteristics

- MC histology: Squamous cell carcinoma (~80% in both arms)
- Most patients were in FIGO stage IIB (43%)
- Median tumor size: 5.0 cm (IQR 4.0–6.0 cm)
- Nodal involvement: ~32% had pelvic node involvement only;

~49–50% had no nodal involvement

- Extended field radiotherapy was planned in only 13% of patients

| | Chemoradiotherapy only group (n=456) | Adjuvant chemotherapy group (n=463) |
|---|---|---|
| Age, years | 45 (38-54) | 46 (37-55) |
| ECOG performance status | | |
| 0 | 344 (75%) | 337 (73%) |
| 1 | 94 (21%) | 117 (25%) |
| 2 | 18 (4%) | 9 (2%) |
| Histological type | | |
| Squamous cell carcinoma | 358 (79%) | 383 (83%) |
| Adenocarcinoma | 79 (17%) | 68 (15%) |
| Adenosquamous cell carcinoma | 19 (4%) | 12 (3%) |
| FIGO 2008 stage | | |
| IB1 (all node positive), IB2, or IIA | 152 (33%) | 154 (33%) |
| IIB | 196 (43%) | 197 (43%) |
| IIIB or IVA | 108 (24%) | 112 (24%) |
| Maximum tumour diameter, cm | 5·0 (4·0-6·0) | 5·0 (4·0-6·0) |
| Nodal involvement | | |
| Pelvic alone | 144 (32%) | 149 (32%) |
| Common iliac alone | 33 (7%) | 31 (7%) |
| Pelvic and common iliac | 44 (10%) | 44 (10%) |
| Neither | 225 (49%) | 231 (50%) |
| Unknown | 10 (2%) | 8 (2%) |
| Extended field radiotherapy planned | | |
| No | 397 (87%) | 404 (87%) |
| Yes | 59 (13%) | 59 (13%) |

**Baseline demographic and disease characteristics**

# Results: Treatment

- 5 cisplatin cycles completed in **~87% patients** in both groups
- **92%** received uninterrupted EBRT, and ~95% received brachytherapy
- HDR brachytherapy was used in **~90%** of cases
- Treatment completed (5 chemo + EBRT + brachy) in **77%** of both groups
- Radiation completed within 8 weeks in **~63–64%** of patients
- **22%** of patients did not start adjuvant chemotherapy , mostly due to patient preference
- **70%** completed all 4 cycles of both carboplatin and paclitaxel

| | Chemoradiotherapy only group (n=456) | Adjuvant chemotherapy group (n=463) |
|---|---|---|
| **Chemotherapy** | | |
| Number of cisplatin cycles commenced | | |
| 0–3 | 27 (6%) | 49 (11%) |
| 4 | 46 (10%) | 32 (7%) |
| 5 | 383 (84%) | 382 (83%) |
| Cisplatin cycles completed at full dose with no delays | | |
| Cycle one | 450 (100%) | 451 (99%) |
| Cycle two | 438 (98%) | 434 (96%) |
| Cycle three | 431 (97%) | 423 (95%) |
| Cycle four | 420 (95%) | 409 (93%) |
| Cycle five | 383 (88%) | 375 (87%) |
| Cisplatin dose intensity, mg/m² per week | 28 (27–29) | 28 (26–29) |
| Radiation technique | | |
| Four field | 413 (91%) | 416 (92%) |
| Two field | 7 (2%) | 5 (1%) |
| Other | 33 (7%) | 33 (7%) |
| **Radiotherapy** | | |
| Mean EBRT dose given, Gy | 45·6 | 45·7 |
| EBRT nodal boost given | 145 (32%) | 135 (30%) |
| EBRT parametrial boost given | 161 (36%) | 165 (36%) |
| EBRT without interruption | 417 (92%) | 418 (92%) |
| Brachytherapy given | 429 (95%) | 426 (94%) |
| Brachtherapy dose rate | | |
| High-dose rate | 393 (92%) | 384 (90%) |
| Low-dose rate | 25 (6%) | 24 (6%) |
| Pulse-dose rate | 9 (2%) | 16 (4%) |
| Not recorded | 1 (<1%) | 4 (1%) |
| Brachytherapy prescription | | |
| Point A | 292 (64%) | 292 (63%) |
| Image-guided | 134 (29%) | 131 (28%) |
| Not recorded | 30 (7%) | 40 (9%) |
| Duration of radiation | | |
| <8 weeks | 278 (63%) | 281 (64%) |
| 8–10 weeks | 141 (32%) | 143 (33%) |
| >10 weeks | 19 (4%) | 14 (3%) |
| **Chemoradiotherapy completed** | | |
| Five cisplatin cycles, 45 Gy EBRT, and brachytherapy | 353 (77%) | 356 (77%) |
| Minimum four cisplatin cycles, 45 Gy EBRT, and brachytherapy | 396 (87%) | 383 (83%) |

**Chemoradiotherapy adherence in the intention-to-treat population**

# Results: Adverse Events

| Adverse Event | Adjuvant Chemotherapy (n=361) | Chemoradiotherapy Only (n=453) |
|---|---|---|
| Grade ≥2 AEs | 356 (99%) | 409 (90%) |
| Grade ≥3 AEs | 292 (81%) | 280 (62%) (p<0.0001) |
| Grade 3–4 AEs (most common) | | |
| ↓ Lymphocytes | 211 (58%) | 208 (46%) |
| ↓ Neutrophils | 71 (20%) | 34 (8%) |
| Anaemia | 66 (18%) | 34 (8%) |
| Serious AEs | 107 (30%) | 98 (22%) |

# Results: Response

| Parameter | Adjuvant Chemotherapy | Chemoradiotherapy Only | p-value |
|---|---|---|---|
| **RECIST 1.1 measurable disease at baseline** | 284/463 (61%) | 252/456 (55%) | – |
| – Complete Response (CR) | 150/284 (53%) | 124/252 (49%) | – |
| – Partial Response (PR) | 77/284 (27%) | 68/252 (27%) | 0.55 |
| **Assessable for PET Response (PERCIST 1.1)** | 244/463 (53%) | 223/456 (49%) | – |
| – Complete Metabolic Response (CMR) | 138/244 (57%) | 111/223 (50%) | 0.14 |

Complete metabolic response on PET CT was associated with **improved 5-year overall survival** ($p<0{\cdot}0001$) and **improved 5-year progression-free survival** ($p<0{\cdot}0001$)

# Results: Survival

- Median duration of follow-up : **60 months**
- 5-year overall survival: 72% (adjuvant chemo) vs 71%

  (CRT only); no significant difference (HR 0.90, **p=0.81**)
- Cervical cancer-specific death: Similar—21% vs 24% **(p=0.21)**
- Progression-free events: 151 (adjuvant) vs 168 (CRT only)
- Median overall survival **not reached** in either group

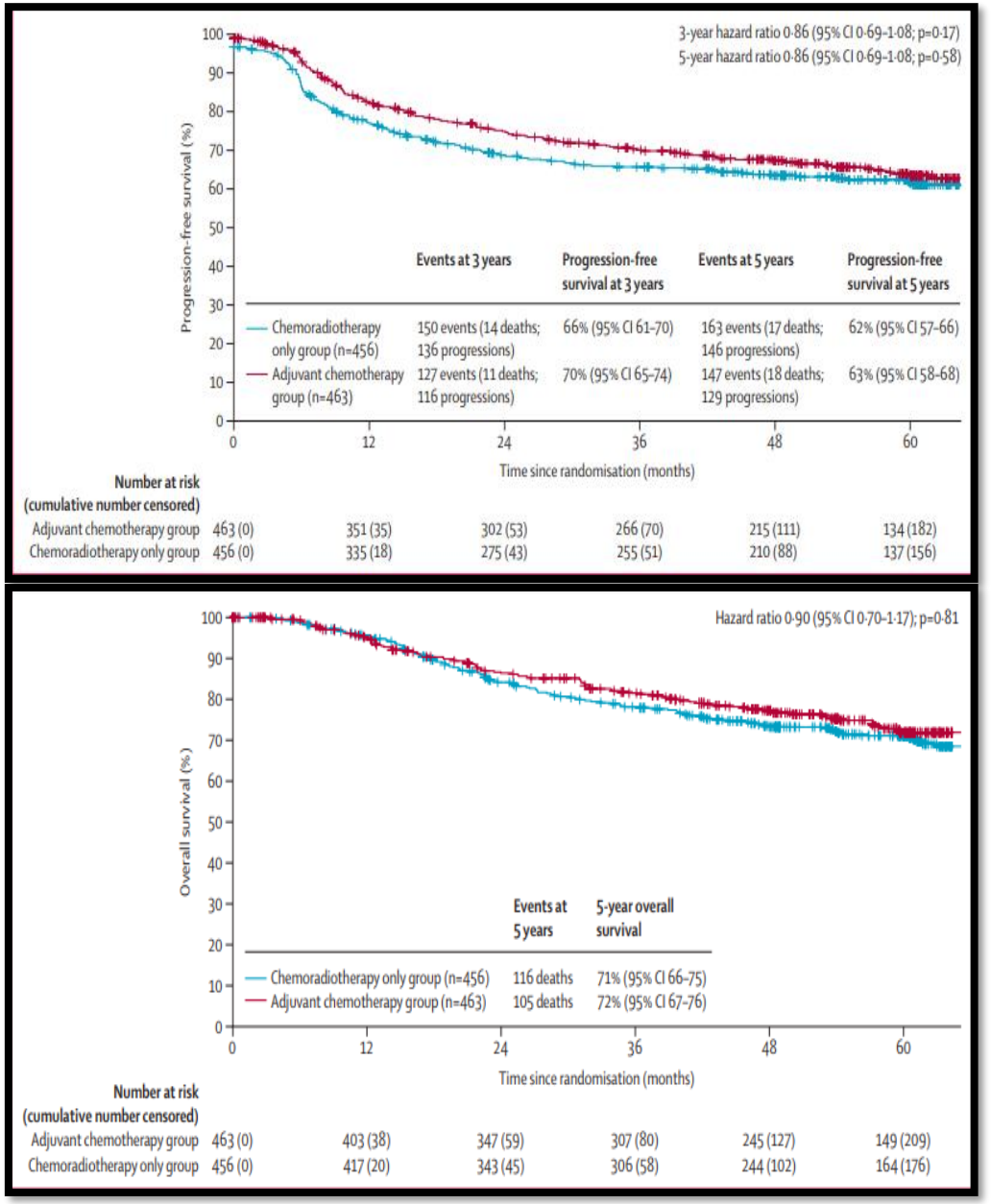
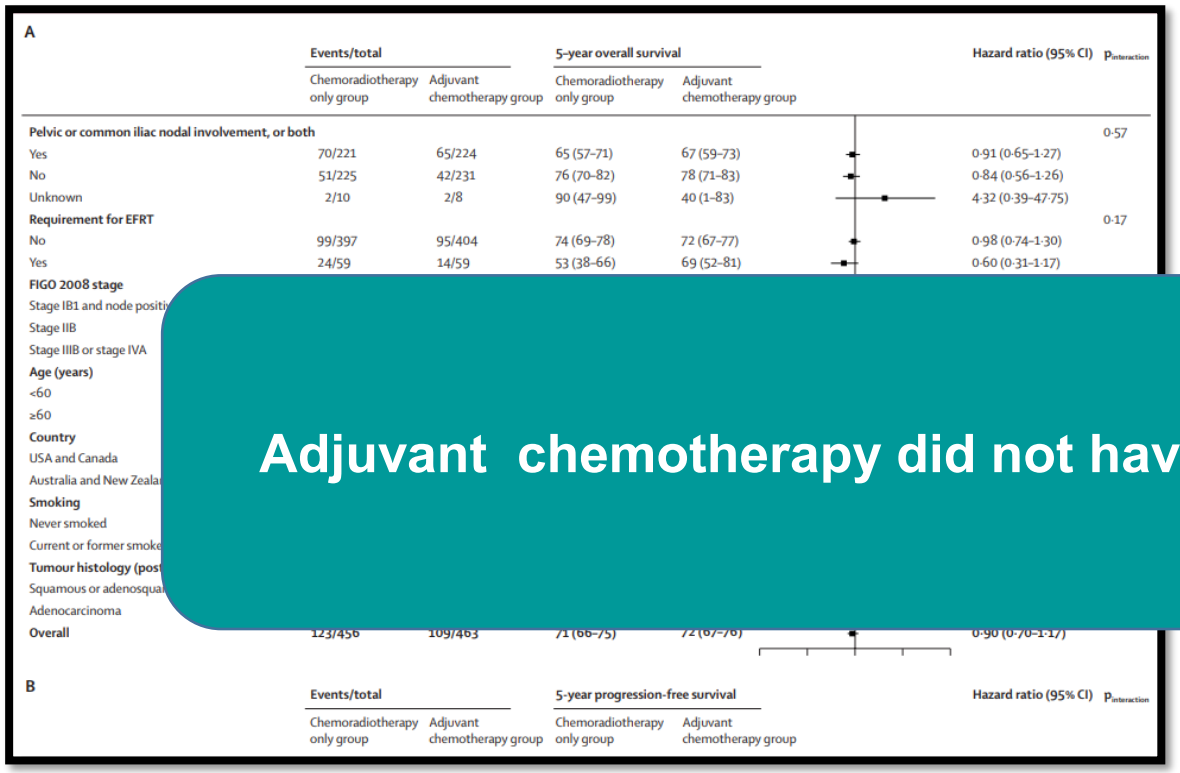



**Figure 2: Kaplan-Meier estimates of PFS & OS**

# Results: Survival



A

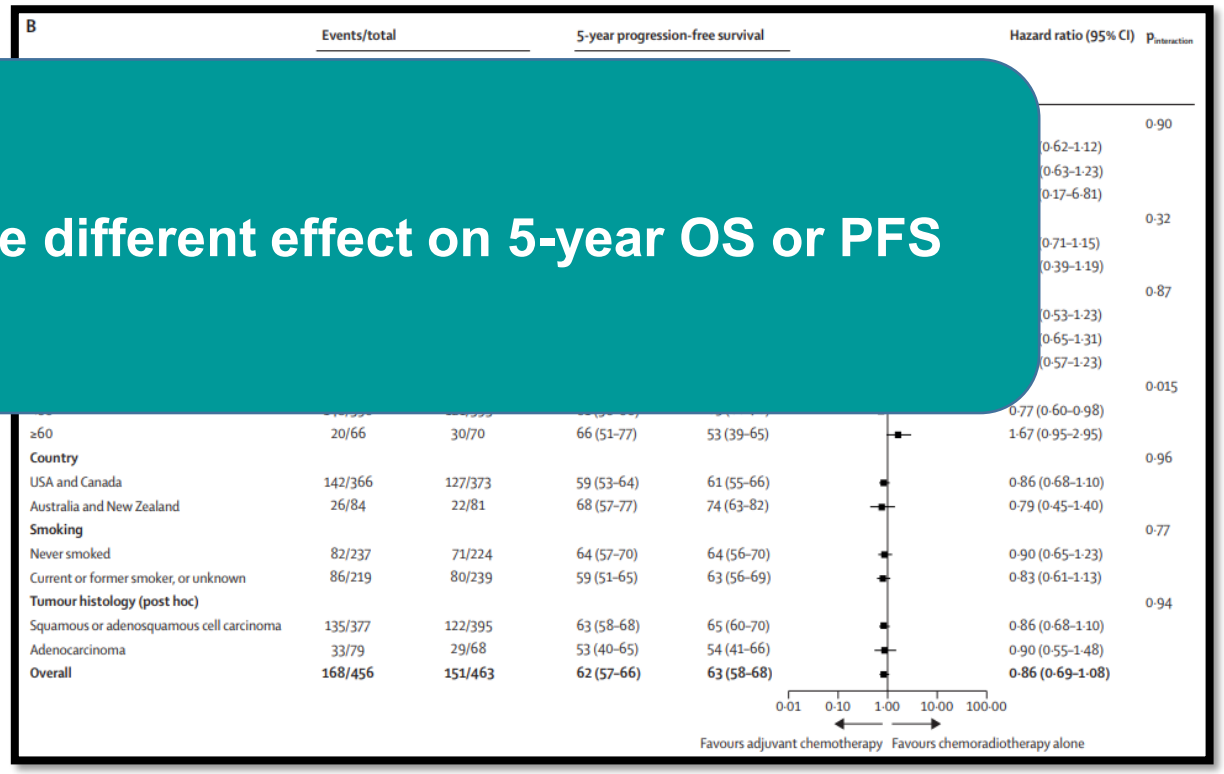
| | Events/total | | 5-year overall survival | | Hazard ratio (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|---|---|
| | Chemoradiotherapy only group | Adjuvant chemotherapy group | Chemoradiotherapy only group | Adjuvant chemotherapy group | | |
| **Pelvic or common iliac nodal involvement, or both** | | | | | | 0·57 |
| Yes | 70/221 | 65/224 | 65 (57–71) | 67 (59–73) | 0·91 (0·65–1·27) | |
| No | 51/225 | 42/231 | 76 (70–82) | 78 (71–83) | 0·84 (0·56–1·26) | |
| Unknown | 2/10 | 2/8 | 90 (47–99) | 40 (1–83) | 4·32 (0·39–47·75) | |
| **Requirement for EFRT** | | | | | | 0·17 |
| No | 99/397 | 95/404 | 74 (69–78) | 72 (67–77) | 0·98 (0·74–1·30) | |
| Yes | 24/59 | 14/59 | 53 (38–66) | 69 (52–81) | 0·60 (0·31–1·17) | |
| **FIGO 2008 stage** | | | | | | |
| Stage IB1 and node positi | | | | | | |
| Stage IIB | | | | | | |
| Stage IIIB or stage IVA | | | | | | |
| **Age (years)** | | | | | | |
| <60 | | | | | | |
| ≥60 | | | | | | |
| **Country** | | | | | | |
| USA and Canada | | | | | | |
| Australia and New Zeala | | | | | | |
| **Smoking** | | | | | | |
| Never smoked | | | | | | |
| Current or former smok | | | | | | |
| **Tumour histology (pos** | | | | | | |
| Squamous or adenosqua | | | | | | |
| Adenocarcinoma | | | | | | |
| **Overall** | 123/456 | 109/463 | 71 (66–75) | 72 (67–76) | 0·90 (0·70–1·17) | |

B

| | Events/total | | 5-year progression-free survival | | Hazard ratio (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|---|---|
| | Chemoradiotherapy only group | Adjuvant chemotherapy group | Chemoradiotherapy only group | Adjuvant chemotherapy group | | |

**Adjuvant chemotherapy did not have different effect on 5-year OS or PFS**

**Forest plots 5-year overall survival**



B

| | Events/total | | 5-year progression-free survival | | Hazard ratio (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|---|---|
| | Chemoradiotherapy only group | Adjuvant chemotherapy group | Chemoradiotherapy only group | Adjuvant chemotherapy group | | |
| | | | | | | 0·90 |
| | | | | | (0·62–1·12) | |
| | | | | | (0·63–1·23) | |
| | | | | | (0·17–6·81) | |
| | | | | | | 0·32 |
| | | | | | (0·71–1·15) | |
| | | | | | (0·39–1·19) | |
| | | | | | | 0·87 |
| | | | | | (0·53–1·23) | |
| | | | | | (0·65–1·31) | |
| | | | | | (0·57–1·23) | |
| | | | | | | 0·015 |
| | | | | | 0·77 (0·60–0·98) | |
| ≥60 | 20/66 | 30/70 | 66 (51–77) | 53 (39–65) | 1·67 (0·95–2·95) | |
| **Country** | | | | | | 0·96 |
| USA and Canada | 142/366 | 127/373 | 59 (53–64) | 61 (55–66) | 0·86 (0·68–1·10) | |
| Australia and New Zealand | 26/84 | 22/81 | 68 (57–77) | 74 (63–82) | 0·79 (0·45–1·40) | |
| **Smoking** | | | | | | 0·77 |
| Never smoked | 82/237 | 71/224 | 64 (57–70) | 64 (56–70) | 0·90 (0·65–1·23) | |
| Current or former smoker, or unknown | 86/219 | 80/239 | 59 (51–65) | 63 (56–69) | 0·83 (0·61–1·13) | |
| **Tumour histology (post hoc)** | | | | | | 0·94 |
| Squamous or adenosquamous cell carcinoma | 135/377 | 122/395 | 63 (58–68) | 65 (60–70) | 0·86 (0·68–1·10) | |
| Adenocarcinoma | 33/79 | 29/68 | 53 (40–65) | 54 (41–66) | 0·90 (0·55–1·48) | |
| **Overall** | **168/456** | **151/463** | **62 (57–66)** | **63 (58–68)** | **0·86 (0·69–1·08)** | |

0·01 0·10 1·00 10·00 100·00

Favours adjuvant chemotherapy Favours chemoradiotherapy alone

**Forest plots 5-year progression-free survival**

# Results: Disease Recurrence

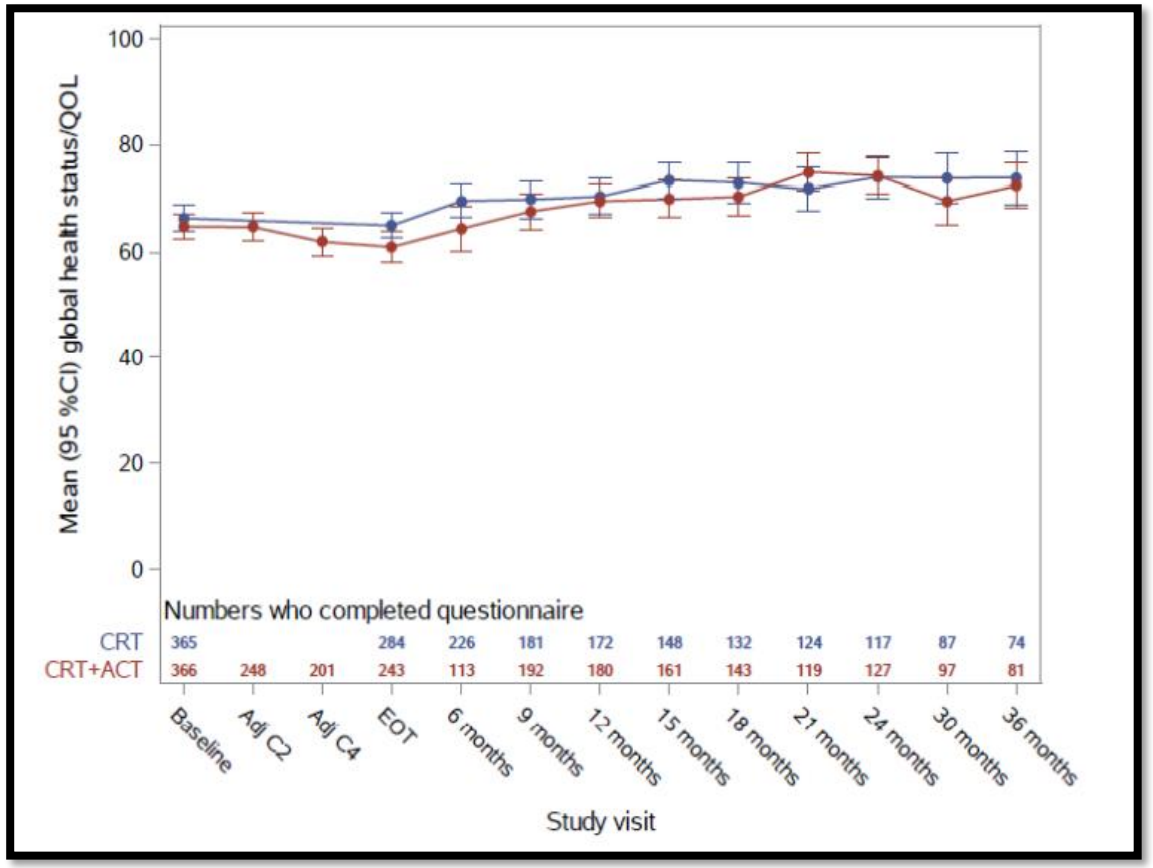
| Type of Recurrence | Adjuvant Chemotherapy (n=463) | Chemoradiotherapy Only (n=456) |
|---|---|---|
| Persistent Disease | 5 (1%) | 15 (3%) |
| Isolated Locoregional | 54 (12%) | 50 (11%) |
| Distant Recurrence | 61 (13%) | 70 (15%) |
| Other/Unknown Recurrence | 11 (2%) | 15 (3%) |

**No evidence of difference** in sites of recurrence (none vs locoregional vs distant vs other or unknown) between the randomly assigned groups (p=0·12)

# Results: HRQOL

- Mean QLQ-C30 global health status and quality of life scores were lower in adjuvant chemotherapy group during the first 3–6 months post-treatment

- However, by 12 to 36 months, scores were comparable between both groups



# Outback Trial : Conclusion

No improvement in survival with adjuvant chemotherapy

High non-compliance with adjuvant therapy

Standard chemoradiotherapy remains the preferred treatment

Future studies should target high-risk patients and address adherence barriers

# Limitations

| | |
|---|---|
| **Open-label design** | • Lack of blinding may have introduced bias in adverse event and quality-of-life reporting |
| **Pre-chemoradiotherapy Randomization** | • Randomization occurred before knowing whether patients could tolerate further therapy, possibly including patients unfit for adjuvant treatment |
| **Selection Limited (IIIA, IIIC2 and requiring interstitial brachytherapy)** | • Might be benefitted by adjuvant treatment |
| **Incomplete treatment** | • Only 77% completed all planned cisplatin cycles, EBRT, and brachytherapy<br>• 22% of patients did not start adjuvant chemotherapy |
| **Local (non-central) response assessment** | • RECIST and PET responses were determined by site investigators, increasing variability |

# Take Home Message

- NACT before CCRT is feasible and lowers distant relapse
- Adjuvant chemotherapy after CCRT  increases toxicity without improving outcomes
- CCRT remains the standard for LACC

## Scope of future Research

**NACT**

- Stage IIIB-IVA, large primary tumour, bulky pelvic/ PALN, tumour infiltrating rectum/bladder

**Adjuvant CT**

- IIIA, IIIC2 and requiring interstitial brachytherapy
- Bulky Residual disease at EBRT completion


# *Thank You*