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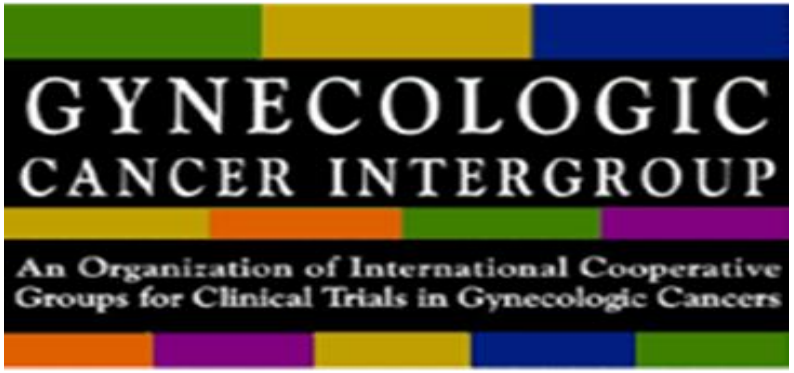

NEOADJUVANT CHEMOTHERAPY IN CERVICAL CANCER

EVA MARÍA GOMEZ GARCIA MD
Medical Oncology

Cervix Cancer Education Symposium, January 2017, Mexico

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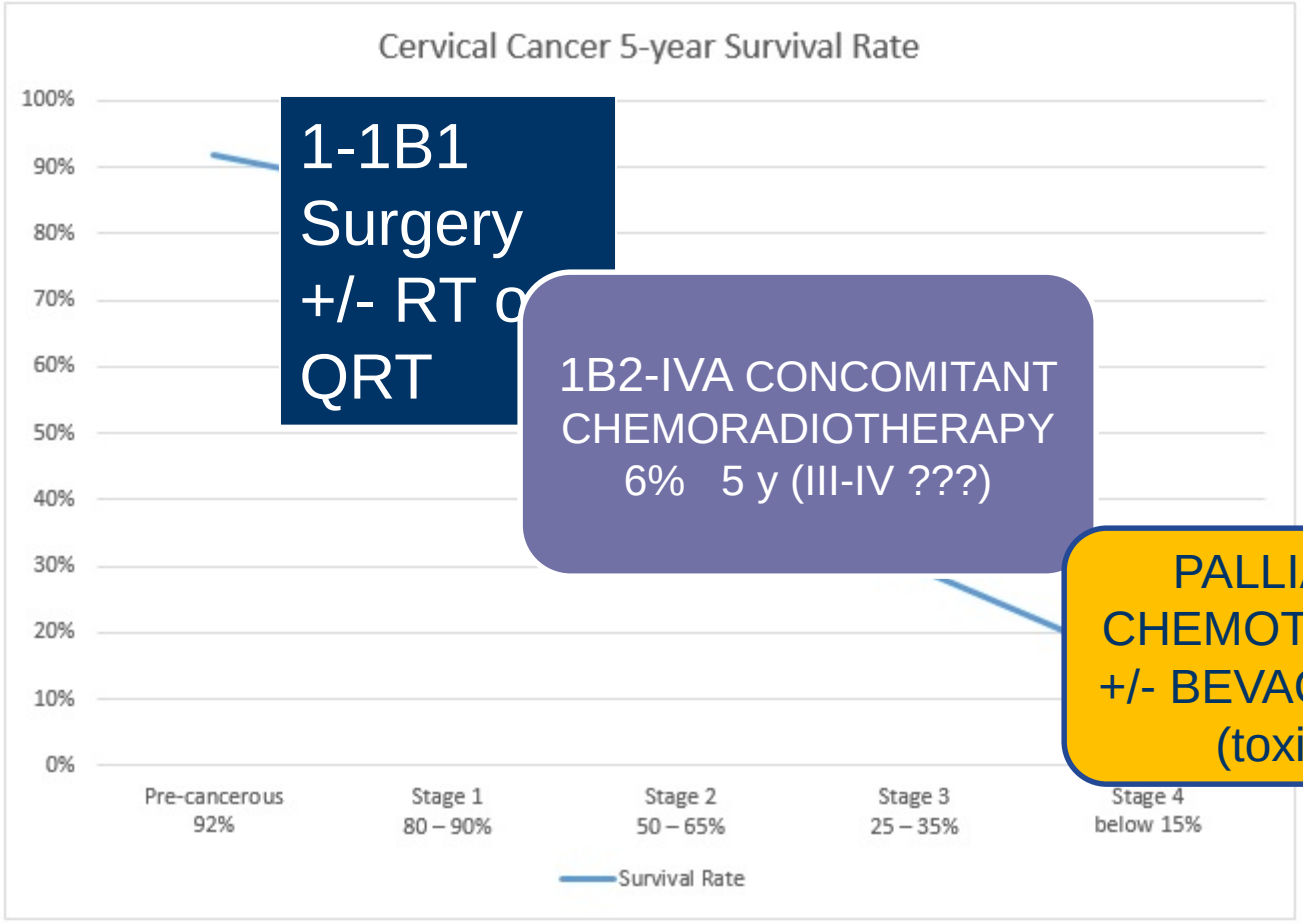

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Table 1 Literature review of prognostic factors for patients treated with CCRT

Author	Year of publication	Patient number	Stage III/IV rate (%)	Prognostic factors
Parker *et al.* (17)	2009			bin
Lim *et al.* (18)	2009			lobin, completion of BRT
Kim *et al.* (20)	2012			onse
Kudaka *et al.* (21)	2012			qlobin
Endo *et al.* (19)				ment, distant metastasis

CCRT, concurrent ch

Tumor size 4 cm

Lymph node enlargement

Perez CA, Grigsby verall treatment period

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Chin J Cancer Res 2016;28(2):221-227

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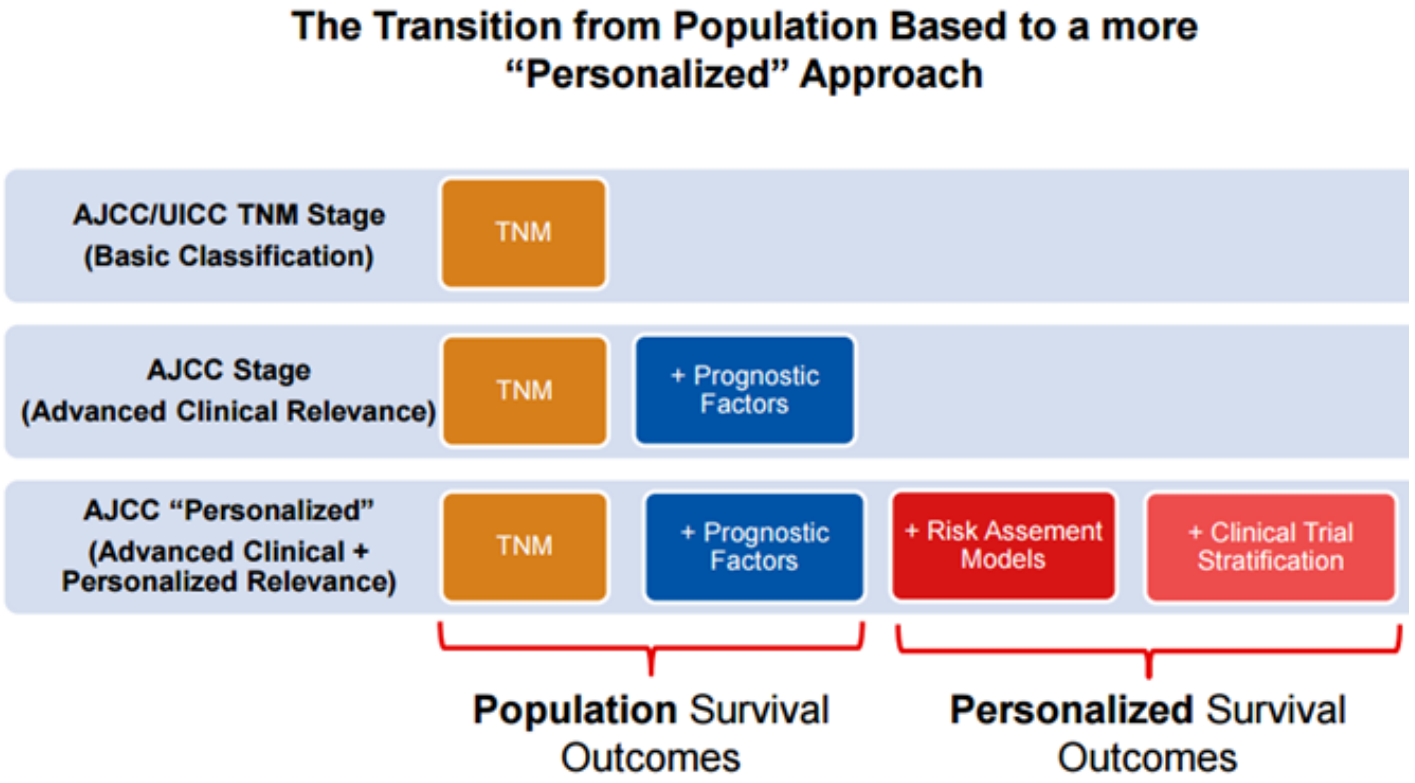
AJCC Vision



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STRATEGIES

1.- Increased peak concentration of cisplatin (CDDP) 89% vs 67% OS 5 y, distant failure 17% vs 23%, toxicity G3/4 39 vs 23%

2.- Surgery after chemo-radiotherapy. Residual disease 14-100%, surgical morbidity acceptable. No randomized trials.

3.- Adjuvant chemotherapy after chemo-radiotherapy. 2 trials Mito-C/5FU No sufficient evidence.

4.- Neoadjuvant chemotherapy before surgery or chemo-radiotherapy.

Cervix Cancer Education Symposium, January 2017, Mexico

Chin J Cancer Res. 2016 Apr; 28(2): 221–227.

RATIONALE FOR THE NEOADJUVANT CHEMOTHERAPY.

1.- Reducing the tumor size,

2.- Expediting the elimination of micrometastasis.

3.- Improving operability

4.-Surgical downstaging.

5. Is associated with fewer side effects than concurrent chemotherapy and radiotherapy.

6. Better response to radiotherapy.

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CHEMOTHERAPY AGENTS USED

Study	Chemotherapy regimen, doses	No. of cycles
Shoji *et al.*, 2013[10]	Carboplatin (AUC6), paclitaxel (175 mg/m^2)/ docetaxel (70 mg/m^2)	2 (18 patients) 3 (5 patients)
Shen *et al.*, 2012[11]	Cisplatin (20 mg/m^2 D1-4)/carboplatin (AUC5), paclitaxel (150 mg/m^2)	2
Yamaguchi *et al.*, 2012[12]	Nedaplatin (80 mg/m^2), irinotecan (60 mg/m^2 D1,8)	3
Pinheiro *et al.*, 2011[13]	Mitomycin C (10 mg/m^2), methotrexate (300 mg/m^2 with folonic acid), bleomycin (15 mg/m^2 D1,8)	4
Vizza *et al.*, 2011[14]	Cisplatin (75 mg/m^2), paclitaxel (175 mg/m^2), ifosfamide (5 g/m^2, mesna)	3
Mossa *et al.*, 2010[15]	Cisplatin (50 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 D1,8)	3
Shoji *et al.*, 2010[16]	Cisplatin (70 mg/m^2), irinotecan (70 mg/m^2 D1,8)	2
Cho *et al.*, 2009[18]	Cisplatin (75 mg/m^2)/carboplatin (AUC5), paclitaxel (135 mg/m^2)	2
Kokawa *et al.*, 2007[19]	Mitomycin-C (10 mg/m^2), irinotecan (100 mg/m^2) D1,8,15 Out of 28 days cycles	2 (28 patients) 3 (7 patients)
Sláma *et al.*, 2007[20]	Cisplatin (50 mg/m^2), ifosfamide (5 g/m^2, mesna)	3
Eddy *et al.*, 2007[21]	Cisplatin, vincristine	3
Choi *et al.*, 2006[22]	Cisplatin (100 mg/m^2), 5-fluorouracil (1000 mg/m^2/day D2-5)	2
Cai *et al.*, 2006[23]	Cisplatin (100 mg/m^2), 5-fluorouracil (1000 mg/m^2/day D2-5)	2
Termrungruanglert *et al.*, 2005[24]	Cisplatin (70 mg/m^2), gemcitabine (1000 mg/m^2 D1,8)	2
Taneja *et al.*, 2005[25]	Cisplatin (50 mg/m^2), bleomycin (15 mg/m^2 D1, 2), vincristine (1 mg/m^2)	3
DeSouza *et al.*, 2004[26]	Cisplatin (60 mg/m^2), methotrexate (300 mg/m^2 with folonic acid), bleomycin (30 mg/m^2 twice weekly)	3

Oncology Reviews 2014; 8:25

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CHEMOTHERAPY AGENTS USED

Napolitano *et al.*, 2003[28]	Cisplatin (50 mg/m^2), bleomycin (15 mg/m^2 D1, 2), vincristine (1 mg/m^2)	3
D'Agostino *et al.*, 2002[29]	Cisplatin (100 mg/m^2), epirubicin (100 mg/m^2), paclitaxel (175 mg/m^2)	3
Benedetti-Panici *et al.*, 2002[30]	Cisplatin (80 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 3 days)	2
Duenas-Gonzalez *et al.*, 2003[31]	Carboplatin (AUC 6), paclitaxel (175 mg/m^2)	3
Duenas-Gonzalez *et al.*, 2002[32]	Cisplatin (100 mg/m^2), gemcitabine (1 mg/m^2 D1,8)	3
Costa *et al.*, 2001[33]	Cisplatin (40 mg/m^2), epirubicin(30 mg/m^2), etoposide(75 mg/m^2), bleomycin (15 mg D1,2)	3
MacLeod *et al.*, 2001[34]	Cisplatin (50 mg/m^2)/carboplatin (AUC5) based combination	3
Aoki *et al.*, 2001[35]	Cisplatin (60 mg/m^2), vinblastine (4 mg/m^2 D1, 2), bleomycin (25 mg/m^2 3 days)	2
Hwang *et al.*, 2001[36]	Cisplatin (50 mg/m^2), vinblastine (6 mg/m^2), bleomycin (25 mg/m^2 3 days)	3
Chang *et al.*, 2000[37]	Cisplatin (50 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 for 3 days)	3
Zanetta *et al.*, 1998[38]	Cisplatin (50 mg/m^2) (75 mg/m^2 in 10 patients), paclitaxel (175 mg/m^2), ifosfamide (5 g/m^2, mesna)	3
Sardi *et al.*, 1997[39]	Cisplatin (50 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 D1-3)	3
Lacava *et al.*, 1997[40]	Vinrolbine (30 mg/m^2 weekly)	4

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RESPONSE TO CHEMOTHERAPY

Neoadjuvant chemotherapy then surgery in locally advanced cervix cancer

Data was collected from 1760 patients enrolled in the above-mentioned studies (22 studies were phase II trials and 8 were phase III trials).

For response:

The ORR was 84%.

Trials that included platinum derivatives ORR of 79%.

Studies that did not include platinum derivatives ORR of 80%,

P value was 0.07.

Down-staging 82%

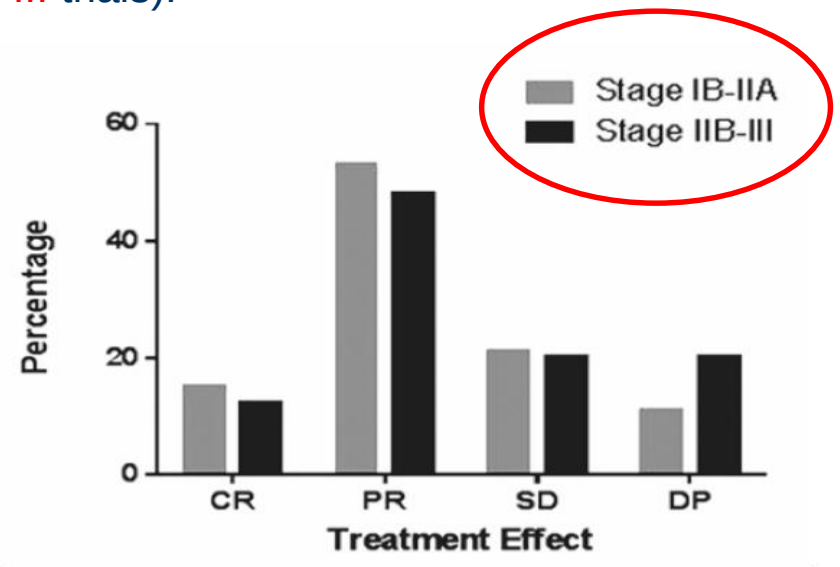

Figure 1. Treatment response by stage. CR, complete remission; PR, partial remission; SD, stable disease; DP, disease progression.

Oncology Reviews 2014; 8:25

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RESPONSE TO CHEMOTHERAPY

Neoadjuvant chemotherapy then surgery or radiotherapy in locally advanced cervix cancer

- Stage IB2 to IIB, 43 patients
- Complete response 39%
- Partial response 51%
- Stable disease 9%
- Down-staging 72%

90%

J Clin Oncol (2002). , 20(1), 179-88.

- Neoadjuvant chemotherapy then chemoradiotherapy phase II
- Respuesta completa 70% post-NACT
- 85% post-QRT.

Br J Cancer 2013 Jun 25; 108(12): 2464–246

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SURGERY

Patients who received neoadjuvant chemotherapy, 90% of them underwent surgery,

The standard operation was radical hysterectomy with pelvic lymphadenectomy (type III, or IV).

5.6% underwent also para-aortic lymphadenectomy due to positive para-aortic lymph nodes

2010
The Cochrane Database of Systematic Reviews curated by the MRC Clinical Trial Unit, London, UK

Resection rate OR, 1.55; 95% CI, 0.96–2.50; p = 0.07

JCOG 0102 N Katsumata, H Yoshikawa

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PROGRESSION FREE SURVIVAL

Neoadjuvant chemotherapy plus QX vs QX or QRT

2010 The Cochrane Database of Systematic Reviews curated by the MRC Clinical Trial Unit, London, UK, 1072 pacientes 1B1-III

PFS (HR, 0.76; 95% CI, 0.62–0.94;

p = 0.01),

- STAGE 1B1-II
- Progression-free survival 59% versus 13% p = 0.02
- Stage III
- PFS : 41.9% vs 36.4%,
- p = 0.29

PFS 68%

. Int J Gynecol Cancer (2011). , 21(1), 92-9

OVERALL SURVIVAL

Neoadjuvant chemo plus surgery vs radiotherapy

Italy stage 1B2-IIB

Overall survival 5y

64.7% vs 18% p = 0.005

Stage IIII

OS : 41.6% vs 36.7%, p = 0.36;

Relative risk of OS QT + QX vs RT

0.63 (95% CI, 0.47–0.86).

Park, Dong Choon MD, PhD Phase II

- OS 2 and 5 years 94 y 89%

J Clin Oncol (2002). , 20(1), 179-88.

Neoadjuvant chemotherapy plus QX vs QX or QRT

Retrospective

476 Patients IB2-IIB

QT + Qx vs QX

OS 1.813; p = 0.0175

QT + Qx versus QRT

OS HR, 3.157; p < 0.0001

2010 The Cochrane Database of Systematic Reviews curated by the MRC Clinical Trial Unit, London, UK, 1072 pacientes 1B1-III

- HR, 0.85; 95% CI, 0.67– 1.07; p = 0.17

. Int J Gynecol Cancer (2011). , 21(1), 92-9

- **NACT + QX radical versus QX radical**

- **Phase III stage IB2, IIA2 y IIB**
- N KATSUMATA
- Bleomicine, vincristine, mitomicin, cisplatin
- 134 patients
- Overall survival 70.0% NACT versus 74.4% surgery group *P*=0.85
- High risk patients NACT 58% vs Qx 80% *P*=0.015
- Many patients received radiotherapy

(JCOG 0102) N Katsumata, H Yoshikawa

- NACT + QX + ADYUVANCIA

OS 5 years 81% and PFS 70%, positive nodes 75% and negative nodes 88%.

Angioli, R Gynecol Oncol (2012).

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NEOADJUVANT CHEMOTHERAPY

18 randomized trials 2074 patients

Interval between cycles

Cycles <14 days HR = 0.83, 95% CI = 0.69 to 1.00, p = 0.046

Cycles >14 days HR =1.25, 95% CI = 1.07 to 1.46, p = 0.005

Intensity of doses of cisplatin

> 25mg/m2 per week HR = 0.91, 95% CI = 0.78 to 1.05, p = 0.20

< 25 mg/m2 per week HR = 1.35, 95% CI = 1.11 to 1.14, p = 0.002

Histologies included squamous cell carcinoma, adenosquamous carcinoma, and/or, adenocarcinoma

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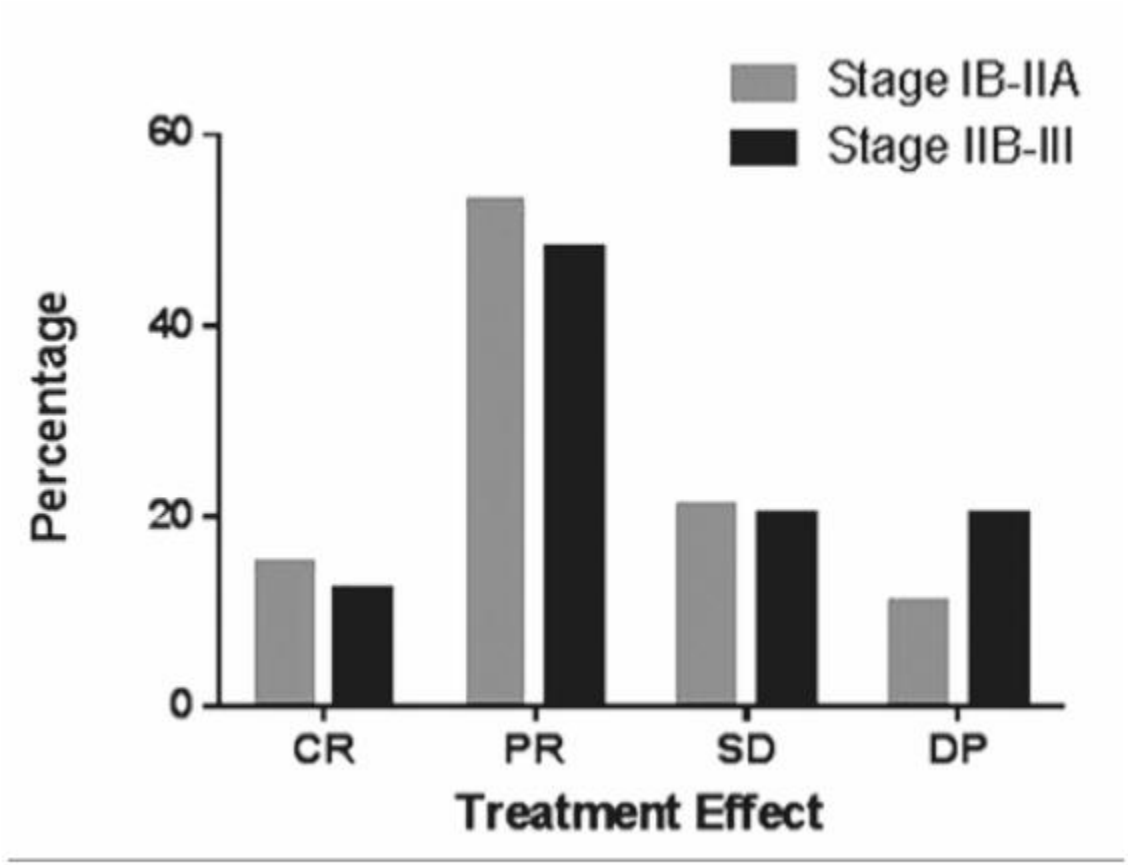

Figure 1. Treatment response by stage. CR, complete remission; PR, partial remission; SD, stable disease; DP, disease progression.

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TOXICITY

- QRT Toxicidad grado 3/4 20% durante la NACT (11% hematologica, 9% no-hematologica)
- Toxicidad grado ¾ 52% durante QRT concomitante (hematologica: 41%, no-hematologica: 22%

- Br J Cancer 2013 Jun 25; 108(12): 2464–246

The combination of chemotherapy followed by surgery is associated with fewer side effects than concurrent chemotherapy and radiotherapy

The study of Tan and Zahra and Green et al.showed grade 3 and 4 late toxicity with a range of 18.3% to 22%, and reported urinary and/or intestinal complications

Angioli, R Gynecol Oncol (2012).

Conclusiones:

MODERADO nivel de evidencia
Heterogeneidad en los estudios.
Brazos de comparacion no optimos
Esquemas de quimioterapia diversos.

Avances:
Ciclos cortos
Dosis densas.
Baja etapa
Mayor resecabiliadad.
Similar toxicidad

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ESTUDIOS CORRIENDO

PHASE III

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