VI CONGRESO ALATRO
Asociación Ibero Latinoamericana de Terapia Radiante Oncológica
HARD ROCK HOTEL CONVENTION CENTER
PUNTA CANA, REPÚBLICA DOMINICANA

Quimioterapia Neoadyuvante en estadíos inoperables

Dra. Marcela de la Torre.

Hospital de Clínicas-Buenos Aires

5-8 de noviembre de 2017

www.alatro2017.grupoaran.com

Introducción

- El cáncer de cuello uterino es el cuarto cáncer más frecuente en mujeres alrededor del mundo y esta cifra aumenta según las regiones geográficas
- La RT mas QT concomitante, con esquemas basados en Pt es el tratamiento estándar para estadíos localmente avanzados desde 1999
- El cáncer de cérvix tiene una moderada tasa de respuesta al Pt y taxanos
- Se consideran estadíos localmente avanzados desde el E IIb al IVa, sin embargo algunos oncólogos incluyen el E Ib2 y E IIa2.

Quimioterapia Neoadyuvante
Inicios

Dadas las tasas de respuesta al Pt en pacientes metastásicos del 50 al 80%, reportadas en esos tiempos, se estudió a fines de los 80s y 90s utilizarlo en neoadyuvancia en un intento de aumentar la sobrevida.

7 Ensayos prospectivos randomizados compararon RT vs QT neoadyuvante mas RT

- Sardi et al. Gynecocol Oncol 1997
- Chang et al . J Clin Oncol 2000
- Benedetti-Pacini J Clin Oncol 2002
- Chauvergnet et al. Bull Cancer 1990
- Kumar et al Gynecol Oncol 1994
- Leborgne et al. Roja 1997
- Souhami et al 1991
- Suedia et al Cancer 1996
- Tattersall et al An J Clin Oncol 1995
- Tattersall et al. Int J Gynecol Cancer 1992

Neoadyuvancia y RT

De estos 7 ensayos

- 5 no demostraron beneficios con la neoadyuvancia
- 2 demostraron una tasa de sobrevida significativamente mejor con RT exclusiva
- Ninguno comparó con RT mas QT concurrente.

Neoadyuvancia mas cirugía en E Ib bulky y E II

Al mismo tiempo y casi los mismos autores exploraron esta modalidad

- Sardi et al
- GOG 2001
- Chang et al
- Benedetti-Pacini

QT neoadyuvante mas Cirugía

- Fue investigada para E Ib bulky y E II en los mismos años utilizando esquemas con Pt
- Los resultados de estos estudios no controlados son muy difíciles de comparar con los resultados de los tratamientos tradicionales debido a que son series pequeñas, con seguimiento muy corto y criterios de selección no claros. No obstante ninguno demostró una ventaja realmente significativa con la neoadyuvancia.
- Y más del 50% de los pacientes operados recibieron RT posterior
- Esto representó una morbilidad importante y un incremento sustancial del costo del tratamiento sin beneficios significativos

Metanálisis: Eur J Cancer 2003
NACT + C vs RT

- 5 estudios
- Positivo para NACT + C. (14% de aumento en sobrevida a 5 años)
- Ninguno usó brazo control de QTRT concomitante (la QT concomitante aumenta aprox lo mismo a la RT exclusiva)
- Los 5 ensayos con RT subóptima por dosis total insuficiente o prolongación del tratamiento
- En uno de ellos 27% de las pacientes no recibieron braquiterapia, 11% menos de 60 Gy al punto A y la dosis media al punto A fue de 70 Gy

Metanálisis 2012 Cochraine
NACT + C Vs C exclusiva

- Incluye trabajos muy antiguos
- Se basó en un pequeño número de ensayos
- Grandes variaciones en los resultados
- Grandes variaciones en RT adyuvante.
- Conclusiones: Por todo lo expuesto a pesar de que NACT obtuvo mejores resultados en SG y SLE, no puede ser recomendada fuera de un ensayo clínico

Radioterapia Postoperatoria Indicaciones

- Ganglios Positivos
- Ganglios Negativos:

  Tumor >4 cm

  Invasión estromal del tercio externo

  Invasión vascular o linfática

  Margenes < de 3 mm o compromeidos

Riesgo de Ganglios Pelvianos (+)
con < 4 mm de invasión (E Ia1) < 5%

Tamaño	Estadío Ib	Estadío IIa
< 1 cm	18%	27%
2 a 3 cm	22%	18%
4 a 5 cm	35%	43%
> 6 cm	50%	38%

Piver et al. 1975

Radioterapia Adyuvante

- Cirugía con Ganglios negativos: 20% de recidivas locales con características de alto riesgo.
- Con Radioterapia adyuvante: 44% de reducción de las recidivas
- Libres de recidivas C: 79%

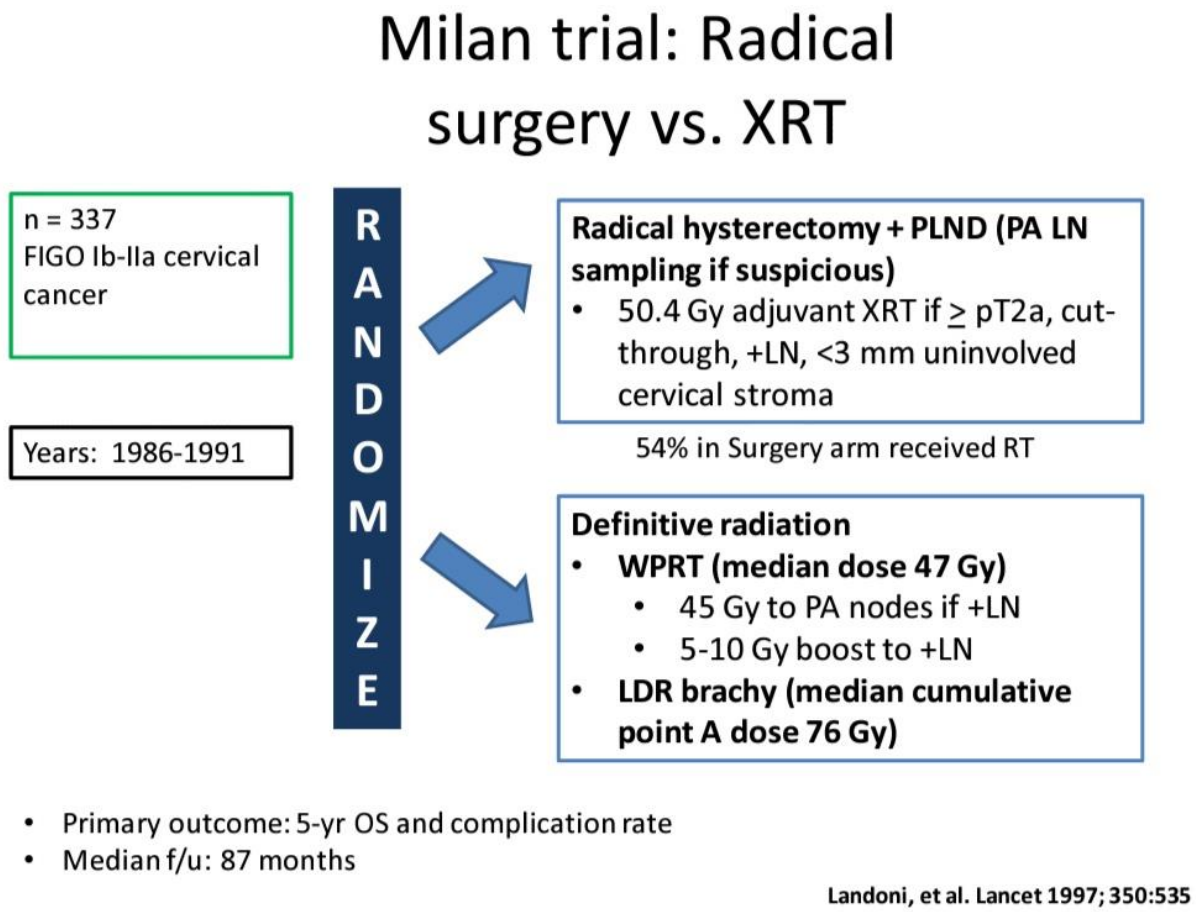
  C + RT: 88%

Radioterapia Adyuvante

Cirugía con Ganglios Positivos la radioterapia reduce las recidivas del 50% al 25% , sobrevida a 4 años 70%

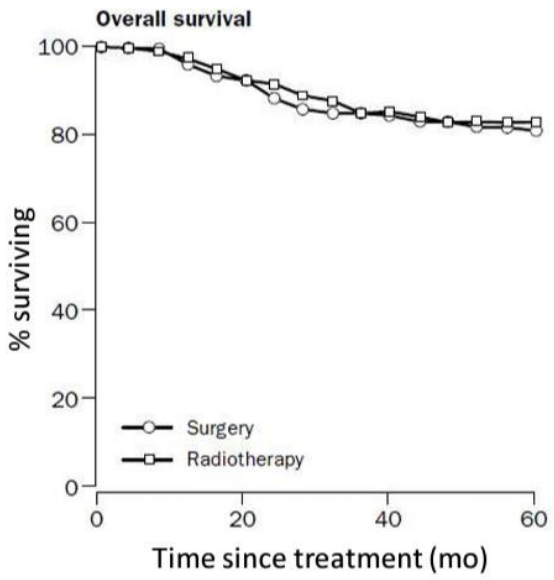
Con Rt + Qt concurrente la sobrevida a 4 años aumenta del 71% al 81%

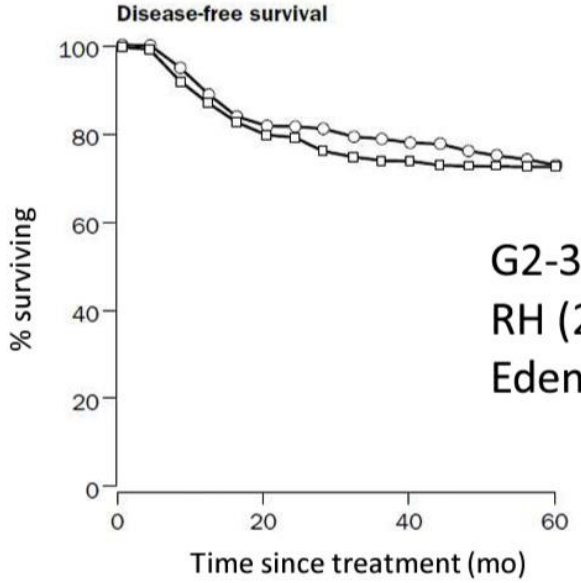
Ya demostrado que mas del 50% requieren RT postoperatoria



Resultados Landoni

No difference in OS or DFS





G2-3 toxicity worse with RH (28% vs 12%, SS)
Edema 9% if RH + PORT

Take Home – Outcomes the same but toxicity worse with RH in bulkier early stage disease

Landoni et al, *Lancet* 1997

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv72–iv83, 2017
doi:10.1093/annonc/mdx220

CLINICAL PRACTICE GUIDELINES

Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Marth[1], F. Landoni[2], S. Mahner[3], M. McCormack[4], A. Gonzalez-Martin[5] & N. Colombo[2], on behalf of the ESMO Guidelines Committee*

[1]Department of Obstetrics and Gynecology, Medical University Innsbruck, Innsbruck, Austria; [2]Department of Gynecologic Oncology, European Institute of Oncology, Milan, Italy; [3]Department of Gynecology and Obstetrics, University of Munich, Munich, Germany; [4]Department of Oncology, University College Hospital, London, UK; [5]Medical Oncology Department, MD Anderson Cancer Center, Madrid, Spain

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: January 2008, last update May 2017. This publication supersedes the previously published version—*Ann Oncol* 2012; 23(Suppl 7): vii27–vii32.

Guía ESMO

Avances de la RT

- Guiada por imágenes tanto externa como braquiterapia
- Aumento de la precisión
- Disminución de la toxicidad en los OR

Sin grandes avances en el tratamiento sistémico

- Continúa siendo de elección el Pt como monodroga o esquemas que lo contengan

Potter, 2007

- 91% control local en T <5cm, igual a los resultados tradicionales
- En >5cm mayor control local 71 a 90% y mejor sobrevida 28 a 58%
- Pero no solo cambia la técnica de braquiterapia (e incluye intersticial) sino también dosis y frecuencia de Qt concomitante

R. Potter et al. R & O, 2007; 83:148-155

- **130 IB-IVA (98-01) 80-85 Gy MRI 2001**
  26pts Interstiticial.

- **V90 medio sin MRI 81Gy, y 90 Gy después.**

- **3a: SLRL 88%. T 2-5cm 96%, T>5cm 71% vs 90% (MRI).**
  Mejoran en supervivencia los T>5cm.

- **Disminución complicaciones al 2% con constraints:**
  75 Gy en 2 cc de recto y sigma
  90 Gy en 2cc vejiga.

RetroEMBRACE
E IIb y IIIb

- Control local del 93% y 79%
- Mejora la sobrevida global a 65% o más
- Baja morbilidad

Table 5. Summary of recommendations

Incidence and epidemiology

- Primary prevention of cervical cancer is now possible via immunisation with highly efficacious HPV vaccines [II, A] and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programs [II, A].

Staging and risk assessment

- Tumour risk assessment includes tumour size, stage, depth of tumour invasion, lymph node status, LVSI and histological subtype. Lymph node status and number of lymph nodes involved are the most important prognostic factors.

Management of local/locoregional disease

Surgery

- Surgical therapy in cervical cancer is adapted to the stage of disease according to FIGO and TNM classification (see Table 2).
- Microinvasive cervical cancer (stage IA1) without LVSI can be managed with conisation or simple trachelectomy to preserve fertility [I, B]. Simple hysterectomy can be offered if the patient does not wish to preserve fertility.
- In stage IA1 with LVSI, surgical assessment of pelvic lymph nodes should be discussed with the patient, including the SLN.
- In patients with FIGO stage IA2, IB and IIA, radical hysterectomy with bilateral lymph node dissection (with or without SLN) is standard treatment, if the patient does not wish to preserve fertility [I, B].
- Increasing evidence suggests an important role for SLND in cervical cancer. Sentinel nodes should be detected on both sides [II, B].
- Surgery should only be considered in patients with earlier stages of cervical cancer (up to FIGO IIA) without risk factors necessitating adjuvant therapy, which results in a multimodal therapy without improvement of survival but increased toxicity [I, A].
- Study results indicate that NACT may offer a benefit over surgery alone in cervical cancer patients, reducing the need for adjuvant RT [I, C].

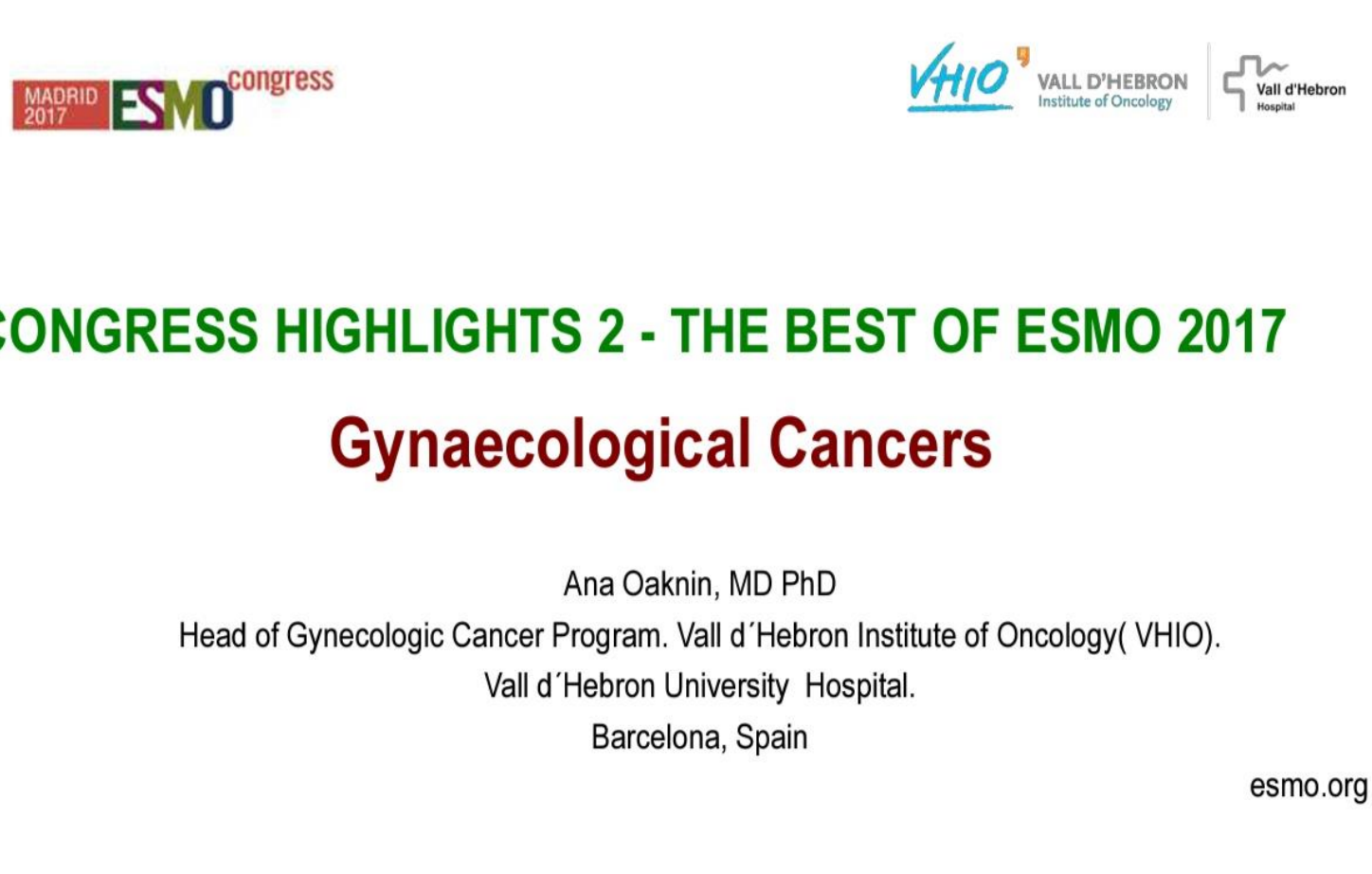
Chemoradiotherapy in locally advanced cervical cancer

- CRT has been the standard of care for patients with bulky IB2–IVA disease for almost two decades, demonstrating an improvement in both DFS and OS with concomitant chemotherapy and RT over standard RT/hydroxyurea [I, A].
- The most commonly used regimen is weekly cisplatin 40 mg/m^2, although the meta-analysis also reported significant benefits with non-platinum agents [I, A].

Adjuvant treatment

- Women with intermediate- and high-risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy (see Table 3).
- Cervical cancer patients with intermediate-risk disease do not need further adjuvant therapy [II, B], whereas adjuvant CRT is recommended in high-risk patients [I, A].

2017


MADRID 2017 ESMO congress
VHIO VALL D'HEBRON Institute of Oncology
Vall d'Hebron Hospital
CONGRESS HIGHLIGHTS 2 - THE BEST OF ESMO 2017
Gynaecological Cancers
Ana Oaknin, MD PhD
Head of Gynecologic Cancer Program. Vall d´Hebron Institute of Oncology(VHIO).
Vall d´Hebron University Hospital.
Barcelona, Spain
esmo.org

Neoadjuvant chemotherapy followed by surgery versus concomitant cisplatin and radiation therapy in patients with stage IB2, IIA or IIB squamous carcinoma of cervix: A randomized controlled trial

Sudeep Gupta, MD, DM, on behalf of

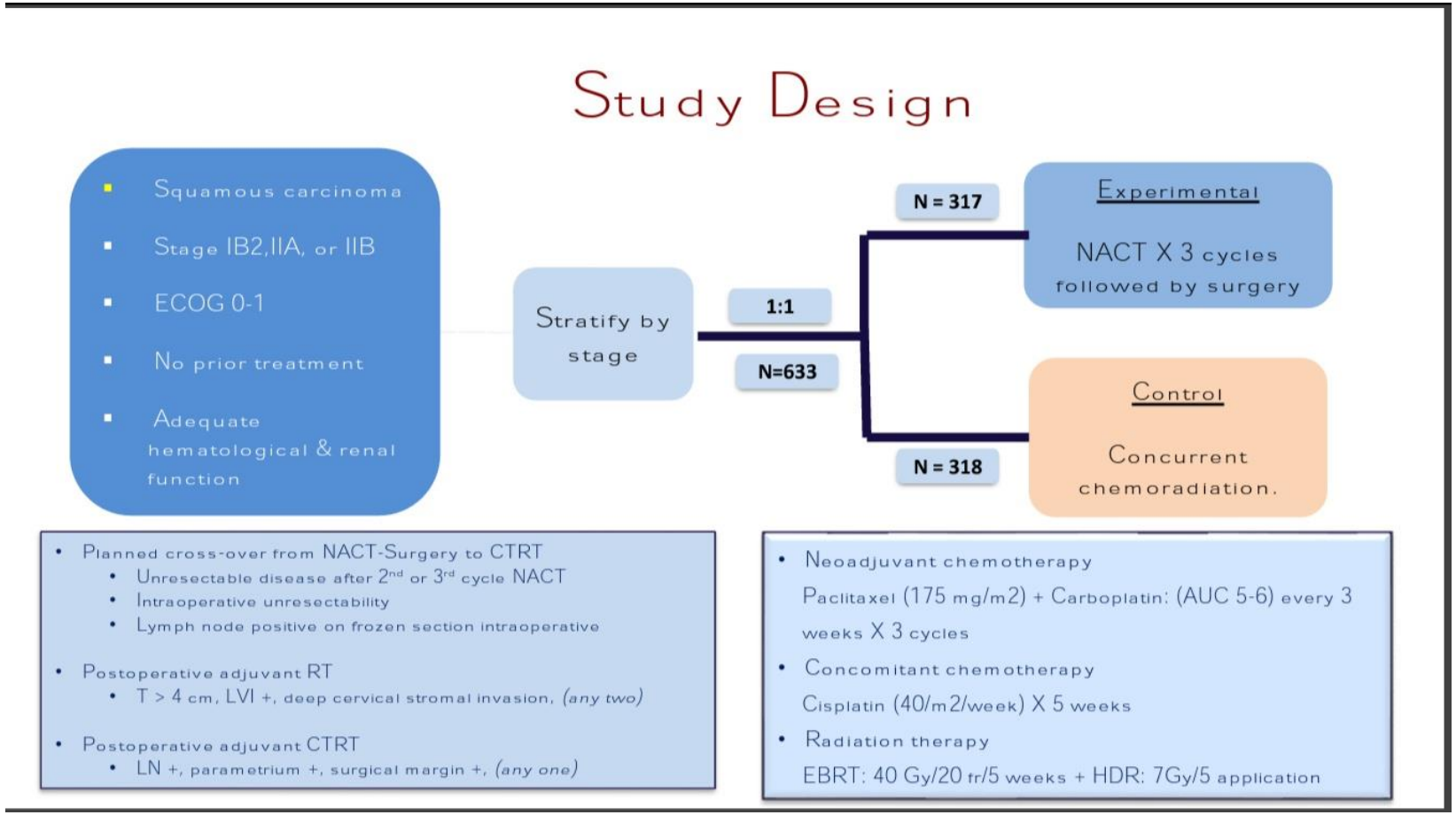
Pallavi Parab, Rajendra Kerkar, Umesh Mahantshetty, Amita Maheshwari, Supriya Sastri, Reena Engineer, Rohini Hawaldar, Jaya Ghosh, Seema Gulia, Swati Godbole, Neha Kumar, Malliga Jeyaraman, Renuka Dalvi, Yogesh Kembhavi, Madhuri Gaikar, Rohit Ranade, Hemant Tongaonkar, Rajendra Badwe and Shyam Shrivastava

Gynaecologic Oncology Group, Tata Memorial Centre, Mumbai

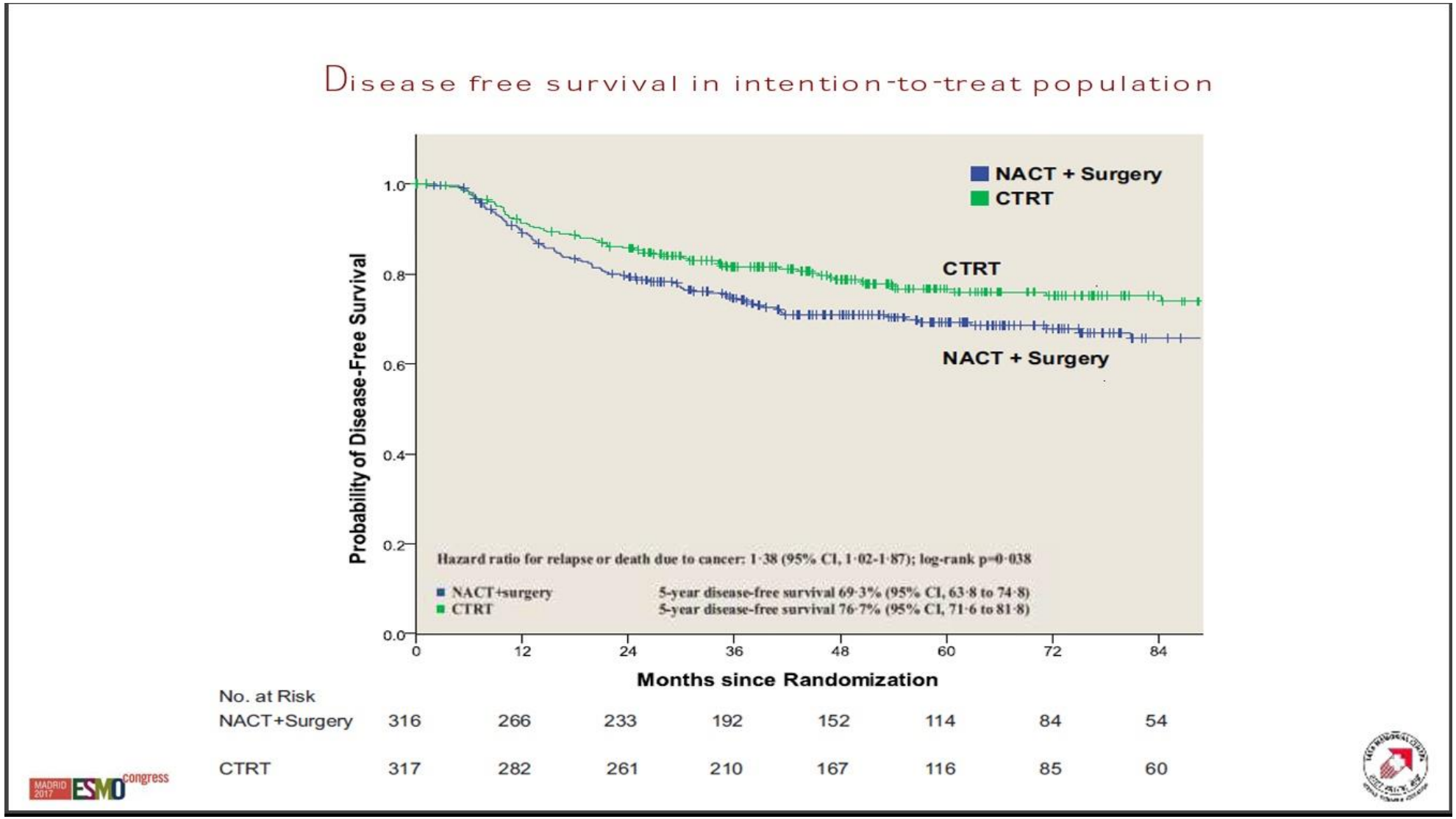
Funded by Tata Memorial Centre, Department of Atomic Energy, Government of India

MADRID 2017 ESMO congress

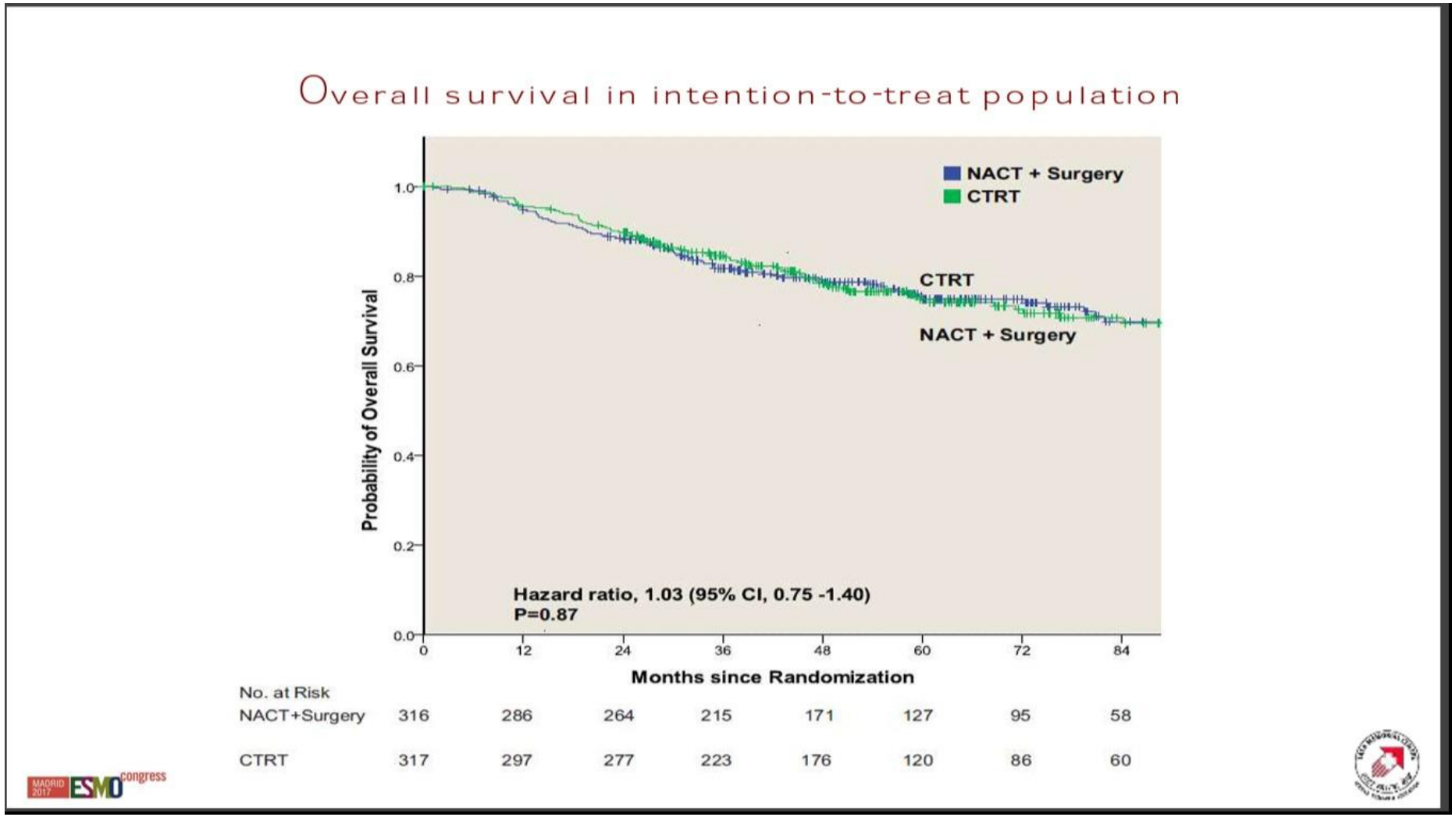
Diseño del Ensayo



Sobrevida Libre de Enfermedad



Sobrevida Global



Conclusiones del trabajo

Conclusions

- Radiotherapy with concomitant weekly cisplatin resulted in higher disease-free survival compared with neoadjuvant chemotherapy using paclitaxel and carboplatin followed by radical surgery in patients with locally advanced squamous cervical cancer.

- Concomitant chemoradiation should continue to be the standard of care in locally advanced cervical cancer.

MADRID 2017 ESMO congress

Conclusiones de la Mesa

MADRID 2017 ESMO congress

THE BEST OF ESMO 2017: GYNAECOLOGICAL CANCERS CONCLUSIONS

- 3-weekly carboplatin-paclitaxel remains the standard-of-care in first-line ovarian cancer treatment: ICON 8 Trial
- The PARP inhibitor, Rucaparib, significantly prolongs median PFS compared to placebo in sensitive relapse ovarian cancer patients: supports the efficacy of PARP inhibitors in ovarian cancer maintenance treatment.
- Concomitant chemoradiation should continue to be the standard of care in locally advanced cervical cancer so far. Waiting for **EORTC 55994 trial results**

A. Clamp et al; 9290_Proffered Paper session: J. Ledermann et al; LBA40_Proffered Paper session:Dr. Gupta et al; 9280_ Presidential Symposium II

Guias NCCN 2007

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Cervical Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

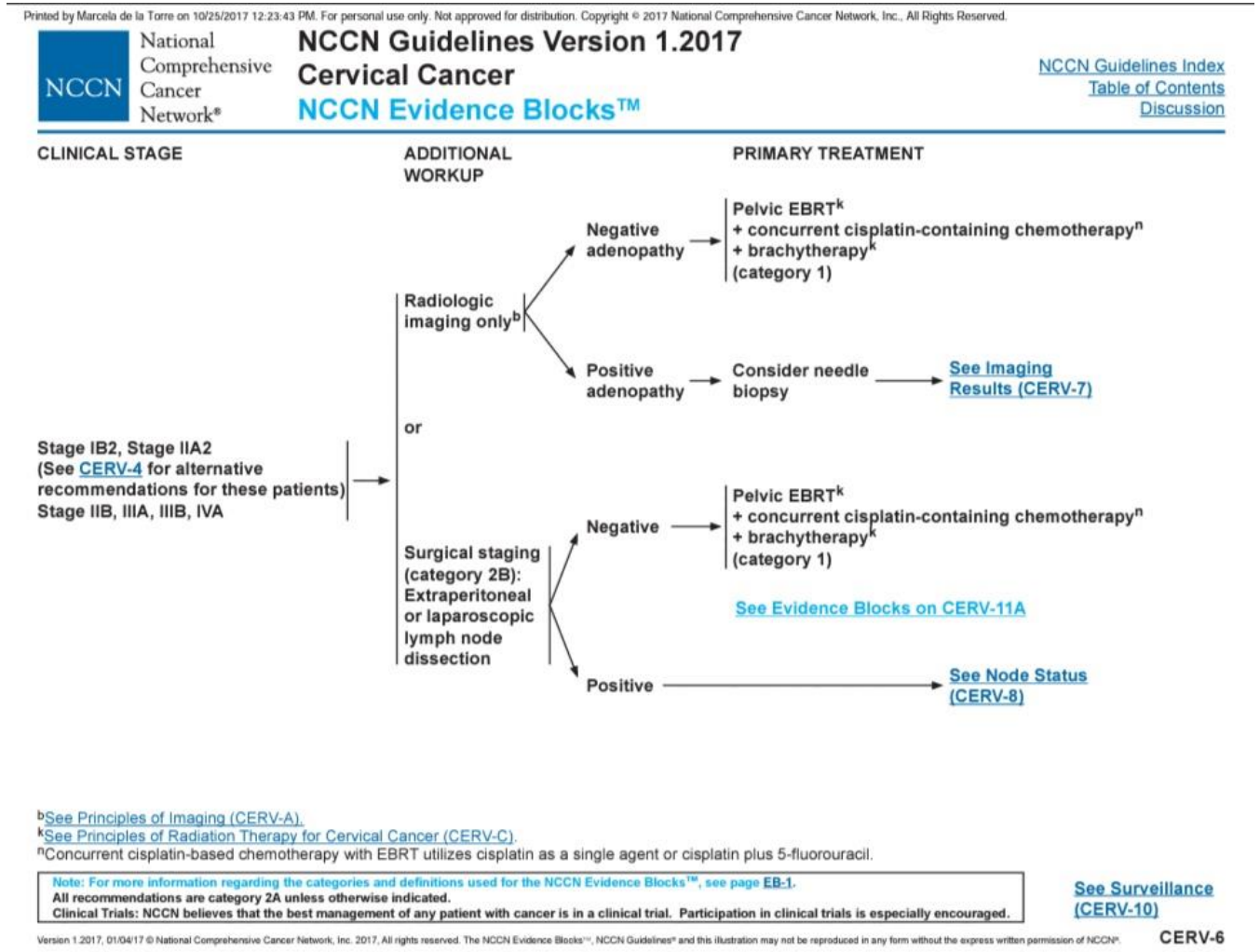
CLINICAL STAGE[b]	PRIMARY TREATMENT (NON-FERTILITY SPARING)	
Stage IB1 and Stage IIA1	Radical hysterectomy + pelvic lymph node dissection[h] (category 1) ± para-aortic lymph node sampling (category 2B) (Consider SLN mapping)[h,i]	See Surgical Findings (CERV-5)
	or Pelvic EBRT[j,k] + brachytherapy (total point A dose: 80–85 Gy)[l,k] ± concurrent cisplatin-containing chemotherapy[n]	See Surveillance (CERV-10)
Stage IB2 and Stage IIA2 (also see CERV-6 for additional recommendations for non-primary surgery patients)	Definitive pelvic EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy (total point A dose ≥85 Gy)[l,k] (category 1 for primary chemoradiation)	See Surveillance (CERV-10)
	or Radical hysterectomy + pelvic lymph node dissection[h] ± para-aortic lymph node sampling (category 2B)	See Surgical Findings (CERV-5)
	or Pelvic EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy[l,o,k] + adjuvant hysterectomy[p] (category 3)	See Surveillance (CERV-10)

See Evidence Blocks on CERV-11A

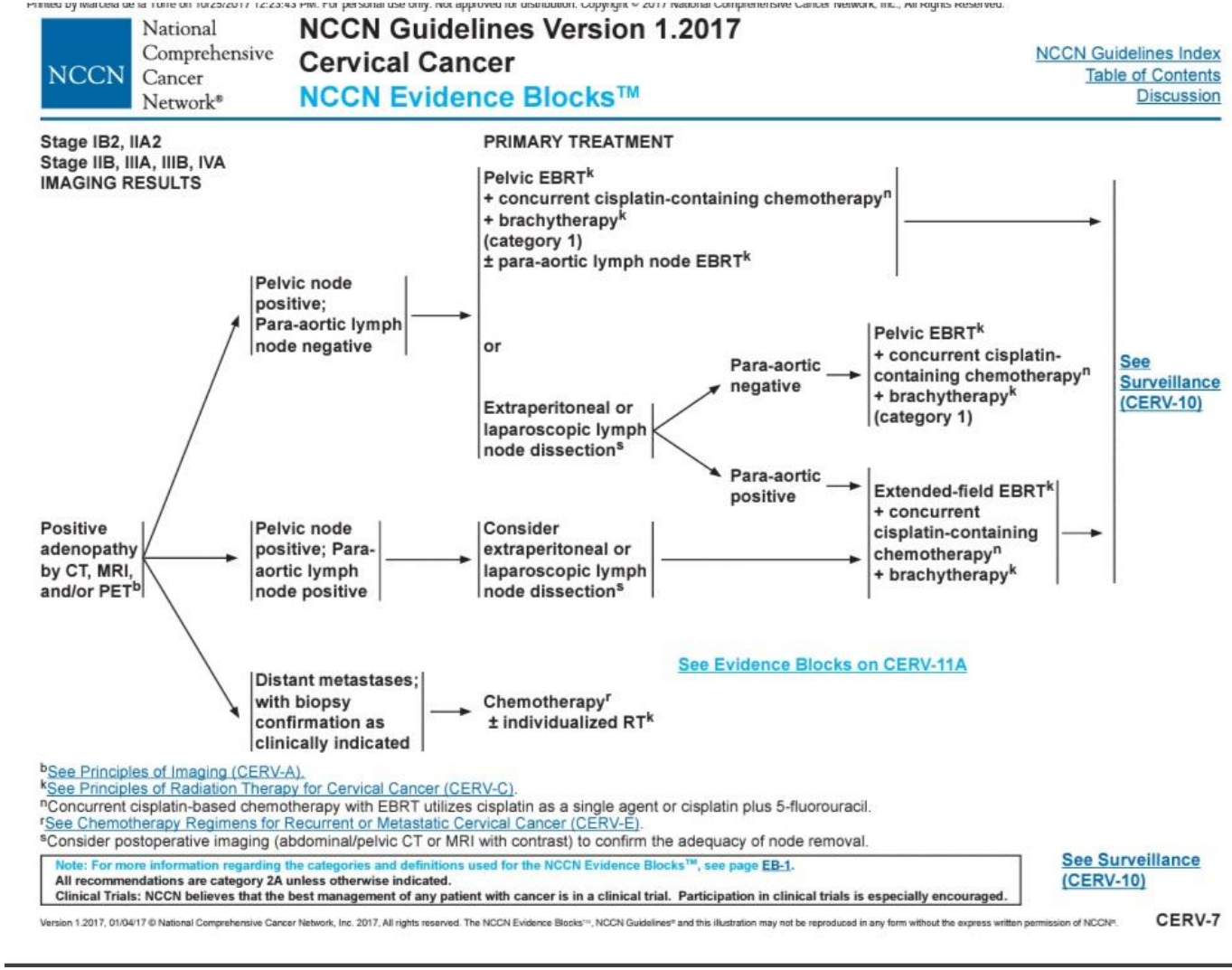
[b] See Principles of Imaging (CERV-A)
[h] See Principles of Evaluation and Surgical Staging (CERV-B).
[i] For SLN mapping, the best detection rates and mapping results are in tumors <2 cm.
[j] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[k] See Principles of Radiation Therapy for Cervical Cancer (CERV-C).
[l] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose-rate (40–70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance, fractionation, and size of target volume. (See Discussion)
[n] Concurrent cisplatin-based chemotherapy with EBRT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[o] The traditional dose would be 75–80 Gy to total point A dose.
[p] This approach can be considered in patients whose extent of disease or uterine anatomy precludes adequate coverage by brachytherapy.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

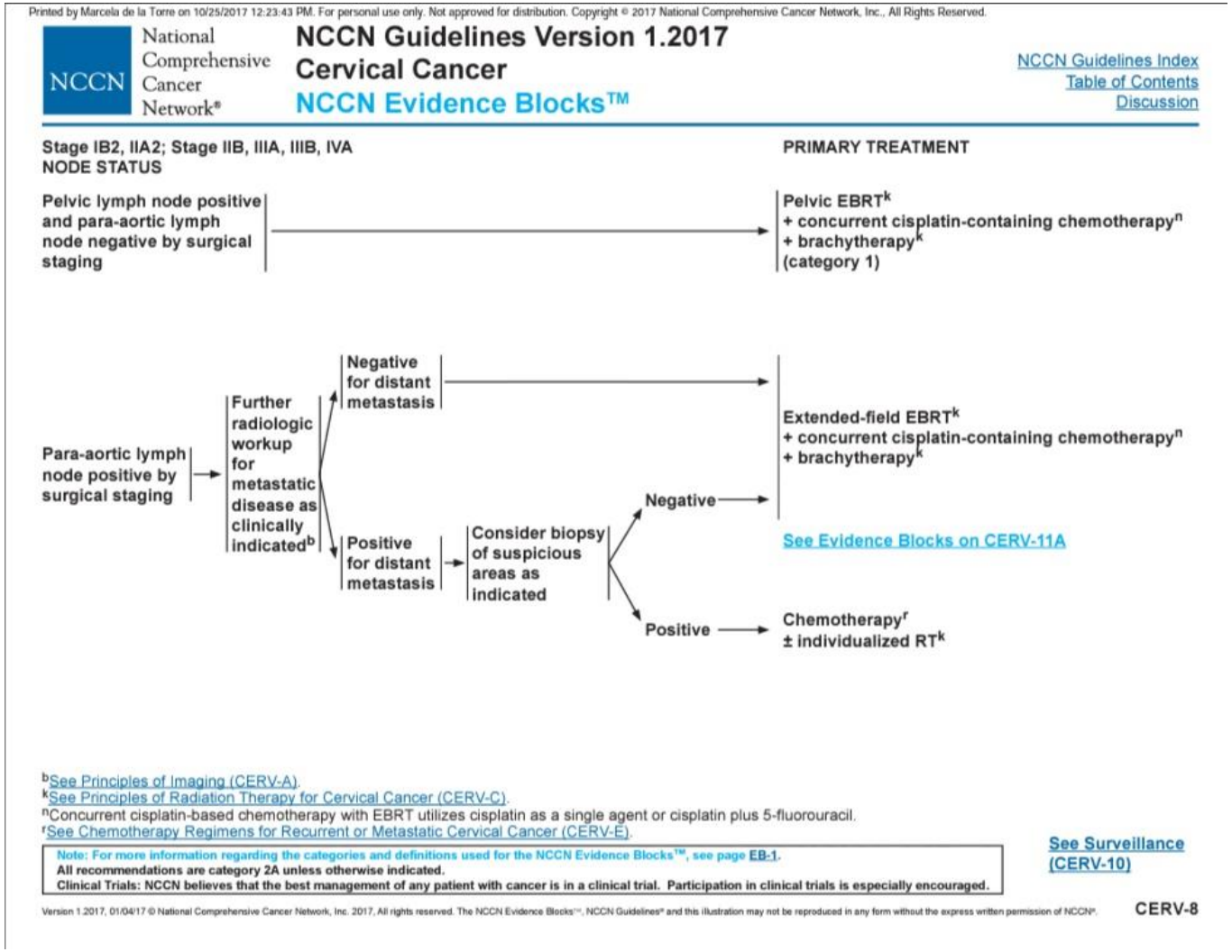
Guias NCCN 2017



Guías NCCN 2017



Guías NCCN 2017



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Cervical Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

Stage IB2, IIA2; Stage IIB, IIIA, IIIB, IVA
NODE STATUS

PRIMARY TREATMENT

Pelvic lymph node positive and para-aortic lymph node negative by surgical staging → **Pelvic EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy[k] (category 1)**

Para-aortic lymph node positive by surgical staging → **Further radiologic workup for metastatic disease as clinically indicated[b]**

- **Negative for distant metastasis** → **Extended-field EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy[k]**
- **Positive for distant metastasis** → **Consider biopsy of suspicious areas as indicated**
  - **Negative** → **Extended-field EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy[k]**
  - **Positive** → **Chemotherapy[r] ± individualized RT[k]**

See Evidence Blocks on CERV-11A

[b] See Principles of Imaging (CERV-A).
[k] See Principles of Radiation Therapy for Cervical Cancer (CERV-C).
[n] Concurrent cisplatin-based chemotherapy with EBRT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[r] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-E).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See Surveillance (CERV-10)

Conclusiones

- Se cumplieron 20 años desde los resultados randomizados comparando cirugía ± RT vs RT sola en estadíos tempranos localmente avanzados de cáncer de cérvix sin diferencias en SLE ni SG
- Cirugía más RT conlleva la peor morbilidad, especialmente a largo plazo
- Guías NCCN-2017: RT definitiva con QT concurrente (categoría 1)

Para encontrar nuestro camino

Necesitamos:

- Jerarquizar la braquiterapia
- un grupo de trabajo latinoamericano
- estudios multicéntricos para poder desarrollar recomendaciones adecuadas a nuestras realidades

Muchas Gracias!!!

Braqui-Argentina