Is there a Role for Neoadjuvant Therapy in Cervical Cancer

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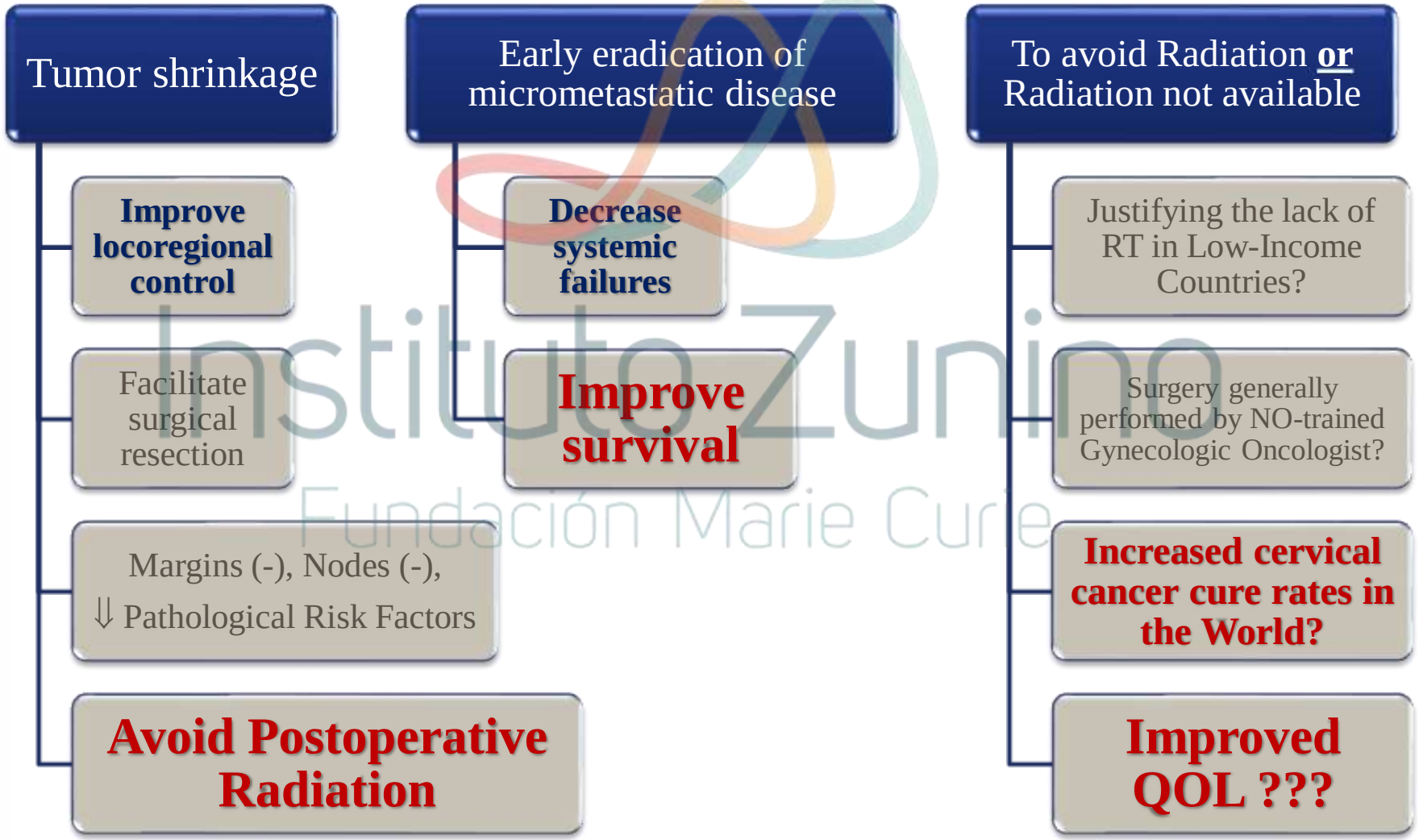
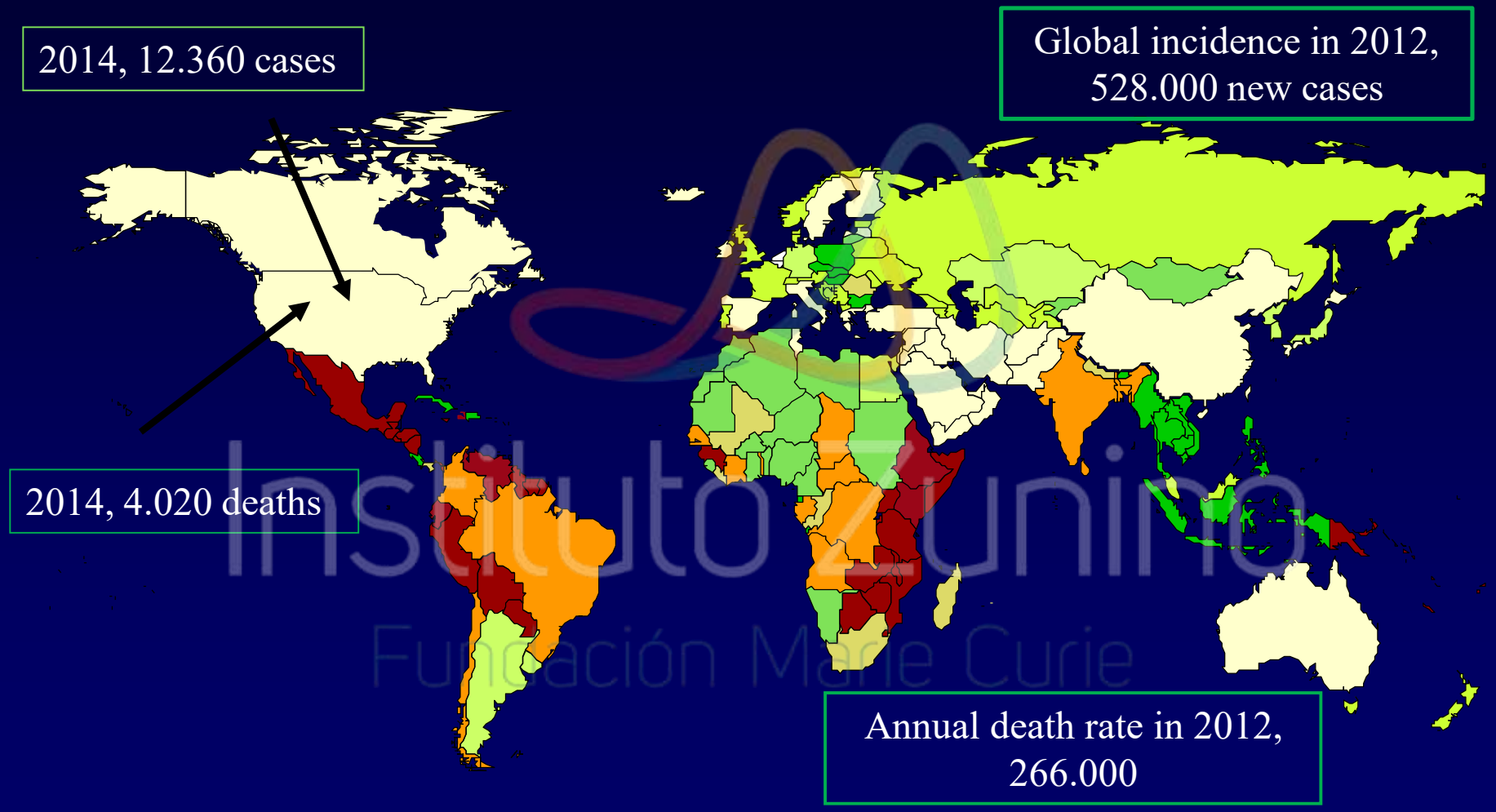
Rationale for Neoadjuvant Therapy



Worldwide incidence of cervical cancer

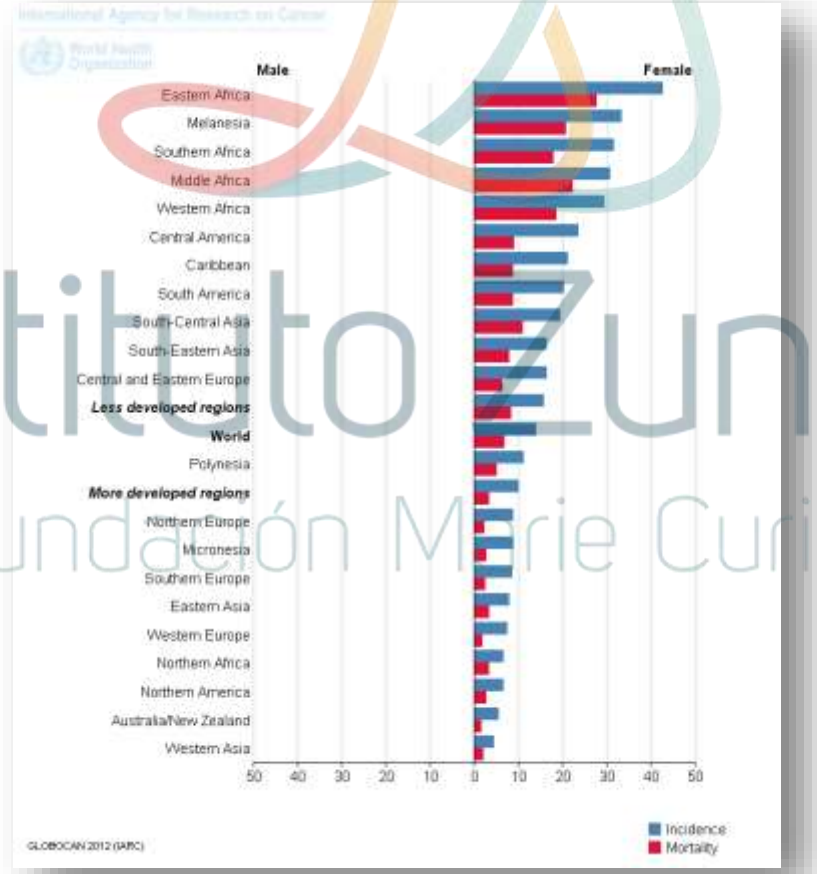


Source : GLOBOCAN 2000; IARC

Estimated Incidence, Mortality and Prevalence Worldwide in 2012

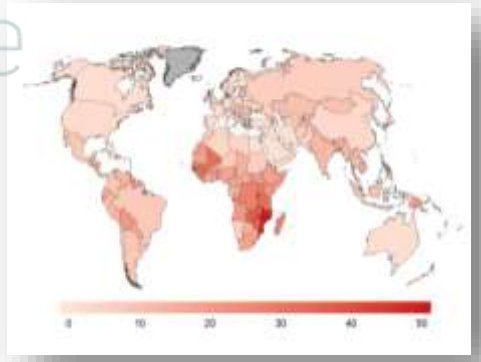
85% of the global burden: less developed regions, where it accounts for almost 12% of all female cancers.

Cervical cancer remains the most common cancer in women in Eastern and Middle Africa.



Incidence Worldwide in 2012

Mortality Worldwide in 2012

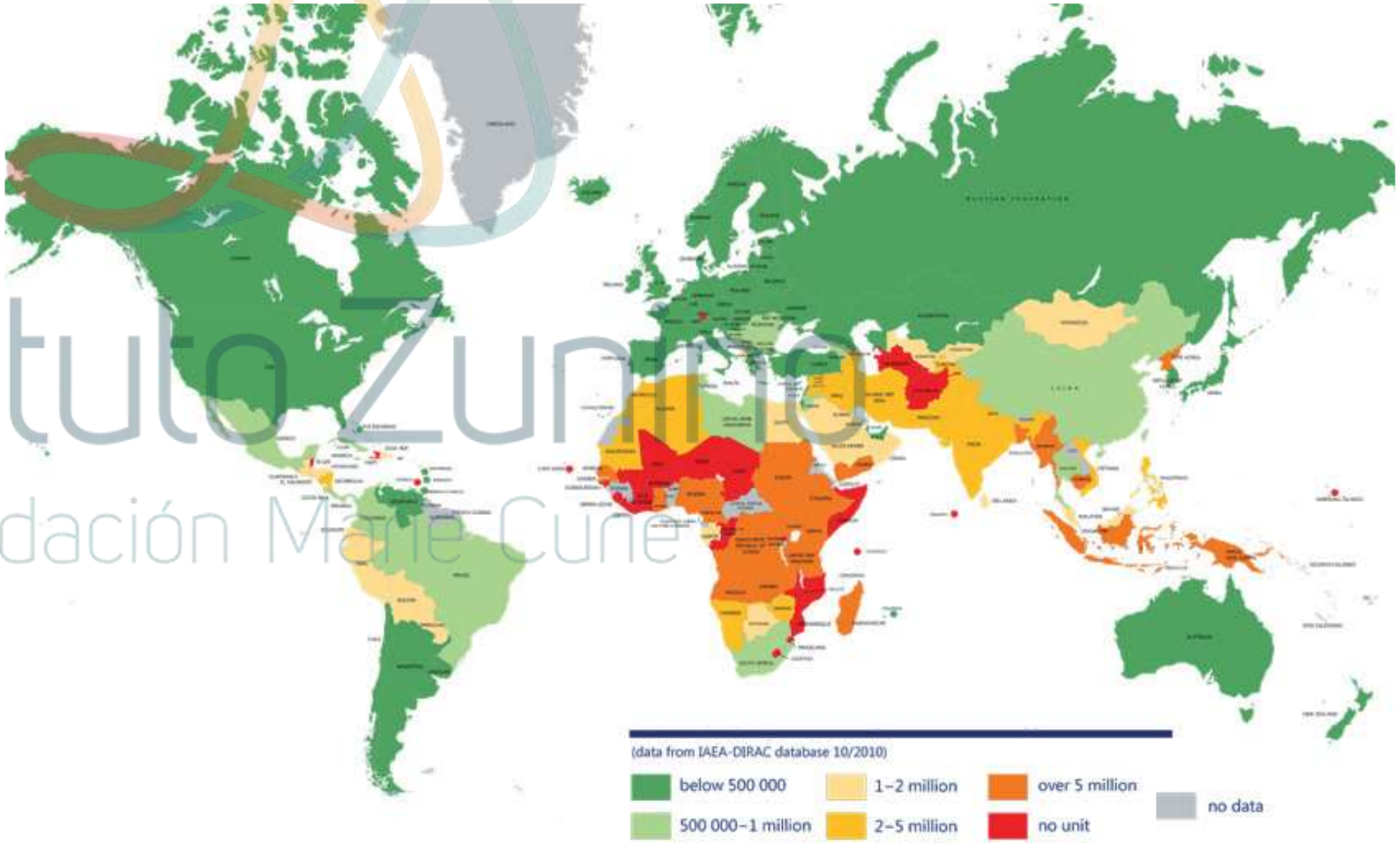


Radiotherapy in Cancer Care: Facing the Global Challenge - IAEA, 2017

E. Rosenblatt & E. Zubizarreta

Directory of Radiotherapy Centers (DIRAC)

- Database including > 7600 RT-Centers, 13000 Teletherapy and 2600 Brachytherapy Units from around the world.
- **High income countries:** 1 RT Unit / 120 000 people.
- **Middle income countries:** 1 RT Unit / 1 million people.
- **Low income countries:** 1 RT Unit / 5 million people.



Revised FIGO Staging System, 2018

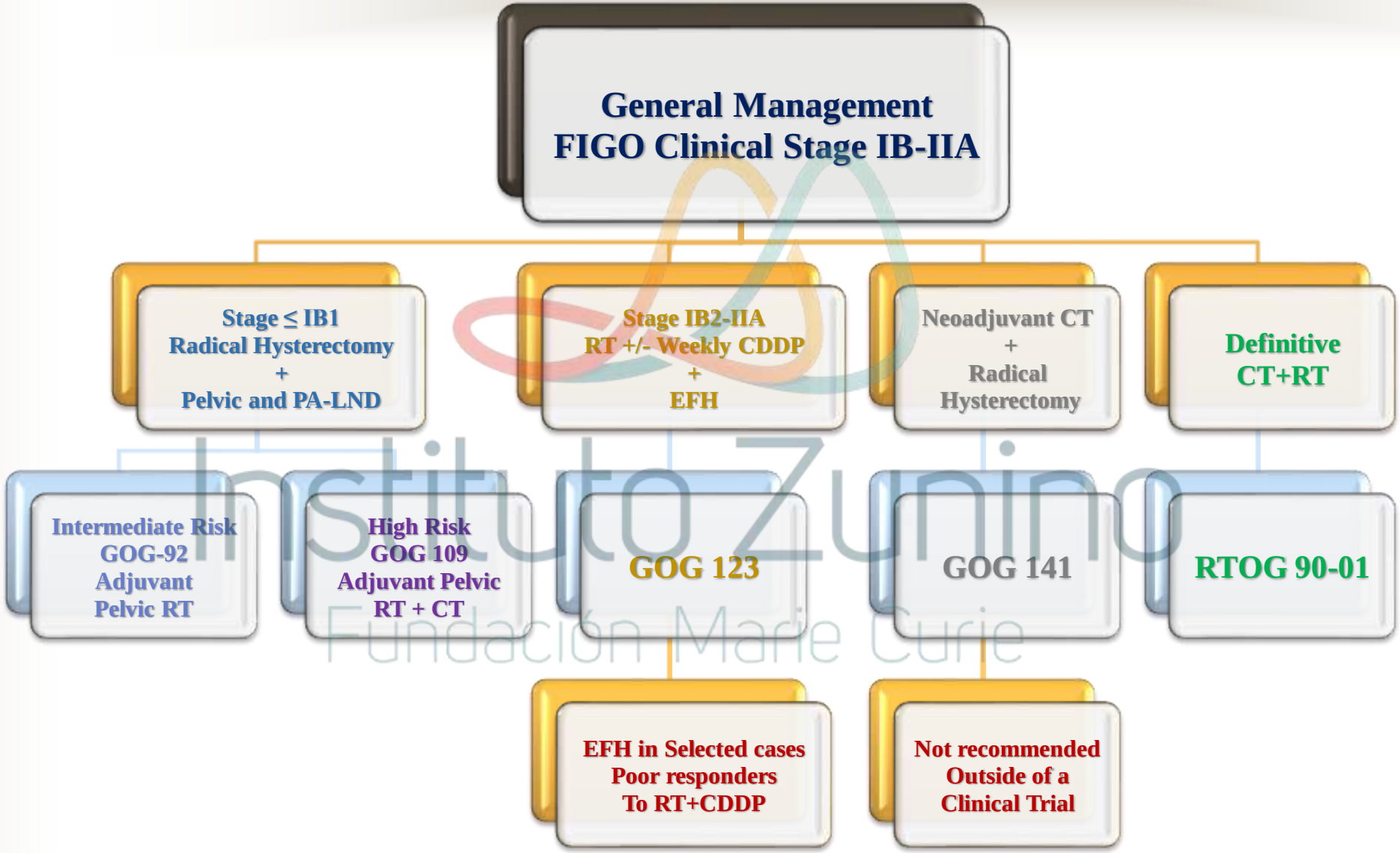
Neerja Bhatla, et. al.
Int J Gynecol Obstet
2018; 143 (Suppl. 2): 22–36

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

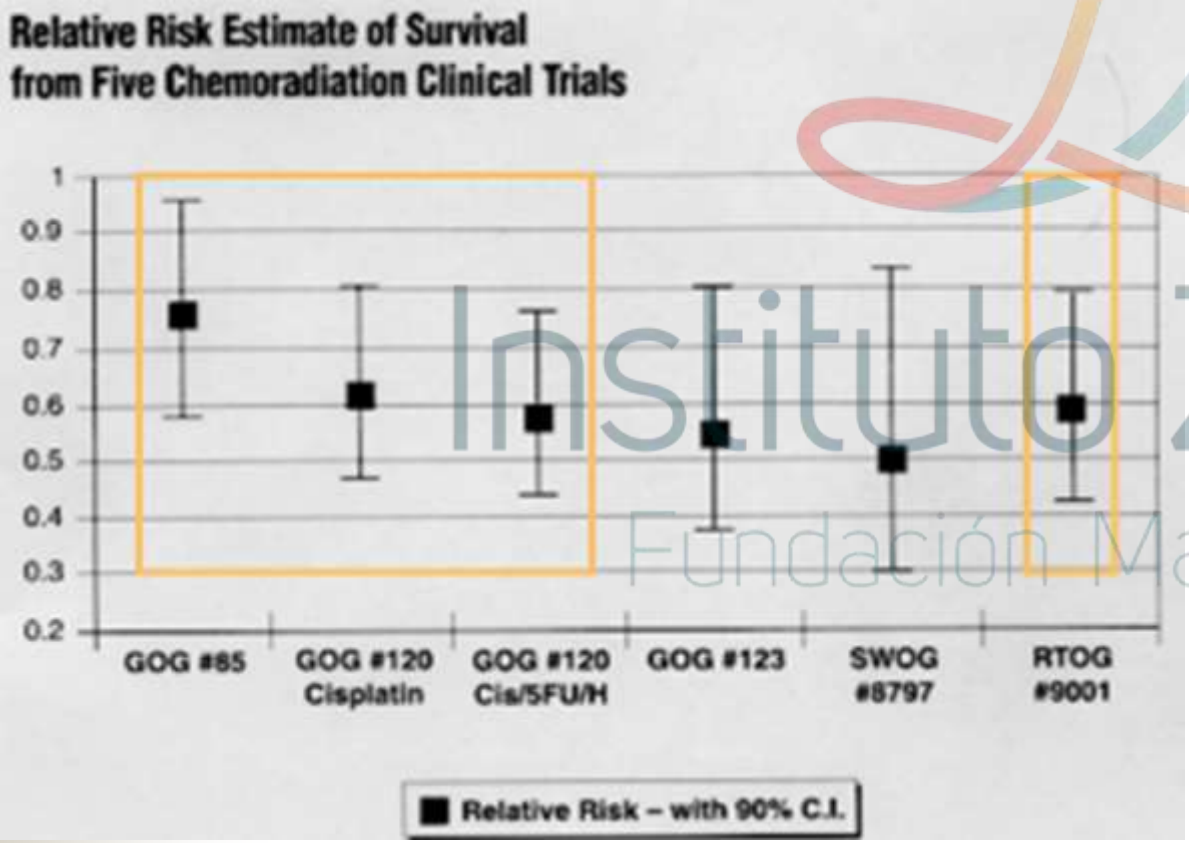
National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Cervical Cancer

CLINICAL STAGE[c]	PRIMARY TREATMENT (NON-FERTILITY SPARING)
Stage IB1 and Stage IIA1	Radical hysterectomy + pelvic lymph node dissection (category 1) ± para-aortic lymph node dissection (category 2B) (consider SLN mapping)[k,l] or Pelvic EBRT[m,n] + brachytherapy (total point A dose: 80–85 Gy)[n,o] ± concurrent platinum-containing chemotherapy[q]
Stage IB2 and Stage IIA2 (also see CERV-6 for additional recommendations for non-primary surgery patients)	Definitive pelvic EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy (total point A dose ≥85 Gy)[n,o] (category 1 for primary chemoradiation) or Radical hysterectomy + pelvic lymph node dissection[k] ± para-aortic lymph node dissection (category 2B) or Pelvic EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n,o,r] + adjuvant hysterectomy[s] (category 3)


General Management
FIGO Clinical Stage IB-IIA
Stage ≤ IB1
Radical Hysterectomy
+
Pelvic and PA-LND
Stage IB2-IIA
RT +/- Weekly CDDP
+
EFH
Neoadjuvant CT
+
Radical
Hysterectomy
Definitive
CT+RT
Intermediate Risk
GOG-92
Adjuvant
Pelvic RT
High Risk
GOG 109
Adjuvant Pelvic
RT + CT
GOG 123
GOG 141
RTOG 90-01
EFH in Selected cases
Poor responders
To RT+CDDP
Not recommended
Outside of a
Clinical Trial

Concurrent chemo-radiation therapy
20 Years Ago !!!!



- Results of five randomized trials led to NIH alert in **1999**:

  "Strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer"

- **However,**
  - **Only 1/3 trials in Advanced disease had a RT alone arm!!!**

    RTOG 90-01

Chemo + RT in Locally or Locoregionally Advanced Cervical Cancer

TRIAL RANDOMIZATION	RISK-GROUP – FIGO cSt # PTS	DFS	OVERALL SURVIVAL
GOG-123; peters, 2000 RT + EFH RT+CT+EFH	FIGO IB2, High Risk - Adjuvant 186 183	4 years 63% 79%, P<0.001	4 years 74% 83%, P=0.008
RTOG- 90 01; Morris, 1999 Pelvic RT + [5FU+CDDP] Pelvic + PA -RT	FIGO Stage: IB, IIA [≥ 5cm or (+) Pelvic LNs], IIB, III & IVA. (-) PA - LN's 195 193 Grade ≥ 3 Acute Toxicity = 45%	5 years 67% 40%, P<0.001	5 years 73% 58%, P=0.004
NCI – Canada; Pearcey, 2000 Pelvic RT + [Weekly CDDP] Pelvic RT	FIGO Stage: IB, IIA bulky; IIB, III & IVA 126 123		5 years 62% 58%, P=0.42
Duenas-Gonzalez, 2011 Pelvic RT + Weekly [CDDP +GEM] + [CDDP+GEM] x 2 Pelvic RT + Weekly CDDP	 259 256 Grade ≥ 3 Acute Toxicity = 85%	5 years (estimate) 74% 65%, P=0.029	5 years (estimate) 76% 65%, P=NS

Locally or Locoregionally Advanced Cervical Cancer

Neoadjuvant RT +/- Chemotherapy
Followed by Extrafascial Hysterectomy

Cervical CA: What is Advanced Stage?

Advanced Cervical Cancer

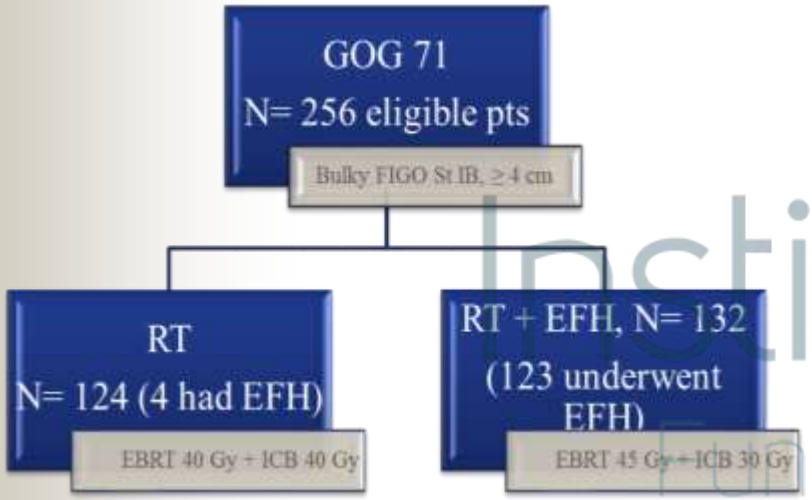
- IB2 or IIA2, tumor **>4cm**, it is often treated as advanced stage (category 1) but also has surgical options (category 2B or 3)
- Parametrial invasion (IIB)
- Distal vaginal invasion (IIIA)
- Pelvic Side wall invasion (IIIB)
- Hydronephrosis IIIB
- Bladder or rectum invasion (IVA)
- Lymph node metastases (St IIIB)

LACC: Prognosis

- Higher rates of recurrence and survival than Stage IA and IB1
- After surgery alone:
  - LRR: ≥ 30%
  - 5-year survival rate: 80% for St IB, to 30-35% for St III

GOG-71: Role of "Adjuvant" EFH in Bulky cSt IB

Keys HM et. al., Gynecol Oncol 89: 343-353, 2003



PFS

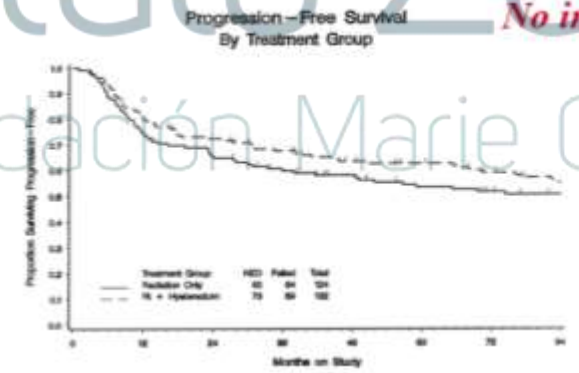
- 23% reduction in the risk of progression
- 5 y- LRR: RT alone, 27%; EFH, 14%
- Distant Failures: RT alone, 16%; EFH, 20%
- No difference in grade 3-4 toxicity (10%)

Survival

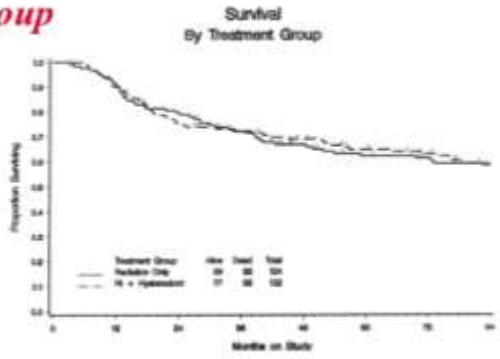
- No difference in overall survival
- 48% and 40% pts had no evidence or microscopic residual disease in the histological specimen, respectively

EFH: lower risk of progression and death for tumor sizes 6-7 cm

No impact in OS for the entire group



256 pts
T ≥ 4 cm



GOG-123: Cisplatin + RT vs RT followed by EFH in Bulky cSt IB

Keys HM et. al., N Engl J Med 340: 1154, 1999

GOG 123
N= 369 eligible pts

Bulky FIGO St IB, ≥4 cm, LN (-)

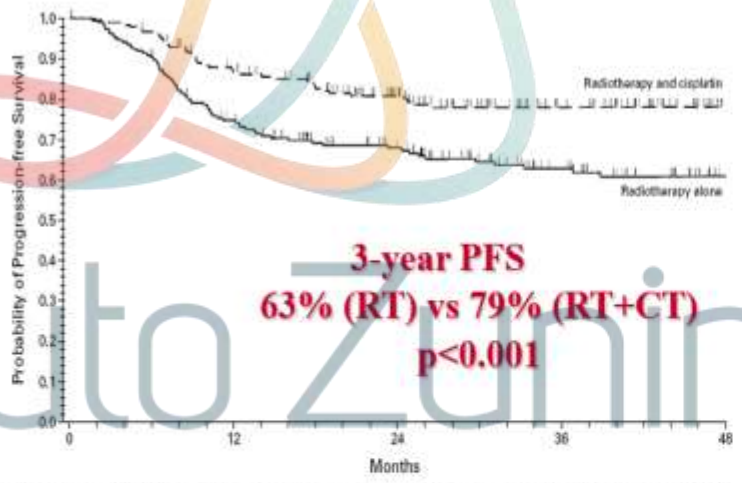
RT Alone
N= 186

EBRT 45 Gy + ICB 30 Gy

RT +
Weekly CCDP
N= 183

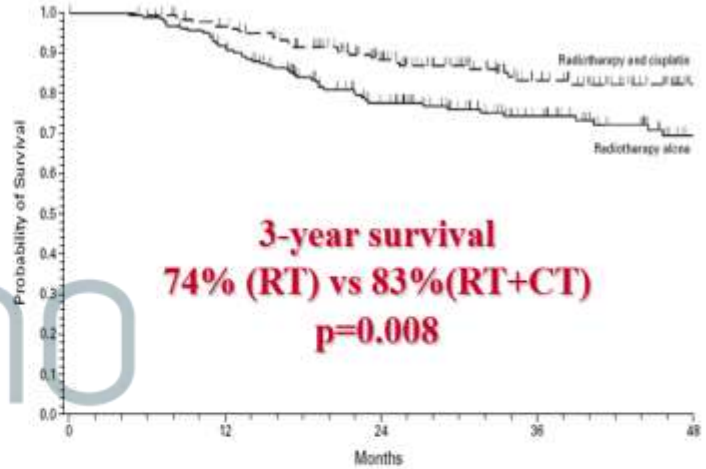
EBRT 45 Gy + ICB 40 Gy

Extrafascial Hysterectomy



3-year PFS
63% (RT) vs 79% (RT+CT)
p<0.001

Figure 1. Kaplan–Meier Estimates of Progression-free Survival in Patients with Cervical Cancer Given Radiotherapy and Cisplatin or Radiotherapy Alone.
The rate of progression-free survival was significantly higher among patients in the combined-therapy group (P<0.001). Tick marks indicate patients with progression of disease.



3-year survival
74% (RT) vs 83%(RT+CT)
p=0.008

Figure 2. Kaplan–Meier Estimates of Overall Survival in Patients with Cervical Cancer Given Radiotherapy and Cisplatin or Radiotherapy Alone.
The rate of survival was significantly higher among patients in the combined-therapy group (P=0.008). Tick marks indicate patients who died.

369 pts with tumors ≥ 4cm, (-) LN's (CT/ Lymphangiogram)
RT + EFH vs RT + weekly CDDP + EFH
Median FU = 36 months

Conclusions – GOG 123

GOG-71: EFH after RT was associated with a significant reduction in the rate of pelvic relapses, without impact in the overall risk of recurrence or overall survival

"It is reasonable to conclude on the basis of the results from GOG-71 and 123 that the elimination of EFH from both regimens would not have affected the increase in survival associated with the use of cisplatin.

Therefore, radiotherapy in combination with cisplatin should be adequate for patients with Bulky St IB cervical cancer."

Summary: EFH after RT+/- CCDP

Complication rate: 15-45%

- Grade 2-3 GI and GU
- Extent of the surgery
- Extent of residual Dz

Improved survival in pts with pCR [subset analysis]

No overall impact in survival

It should be limited to Selected Patients with residual disease at the time of the brachytherapy (after 45 Gy) and **MAY BE** those with adenocarcinomas and/or uterine extension

Locally or Locoregionally Advanced Cervical Cancer

NACt + Surgery

vs

Surgery Alone

NACt + Surgery vs Surgery Alone
Cochrane Database Systematic Review

Rydzewska L et al; 2012;(12):CD007406

6 trials, 1078 women

To assess the role NACt prior to Surgery in women with Early or LACC

Primary outcome: OS

Secondary outcomes: PFS, local and distant recurrence, rates of resection and surgical morbidity

In 5 out of 6 trials: 30-50% of pts received adjuvant RT

NACt was associated with:

- Improved OS and PFS
- Decreased risk of local recurrence **(≈ 50% patients had post-op RT)**
- No difference in distant recurrence and rates of resection **(Wasn't this the rational for induction CT?)**
- Decreased adverse pathological findings: (+) LN, (+) parametrial

Efficacy of NACt followed by Surgery vs Surgery alone in patients with FIGO stage IB1 to IIA Cervical Cancer An International Collaborative Meta-analysis

H.S. Kim. EJSO, 2013; 39: 115

5 RCTs and 4 observational studies
1784 patients
No information regarding the % of pts requiring Adj RT

NACt - FAVORABLE

Lower rates of tumor ≥4 cm and LN (+)

Reduced need of RT

Reduced distant metastasis

NACt – NOT FAVORABLE

No diff. in overall and loco-regional recurrences

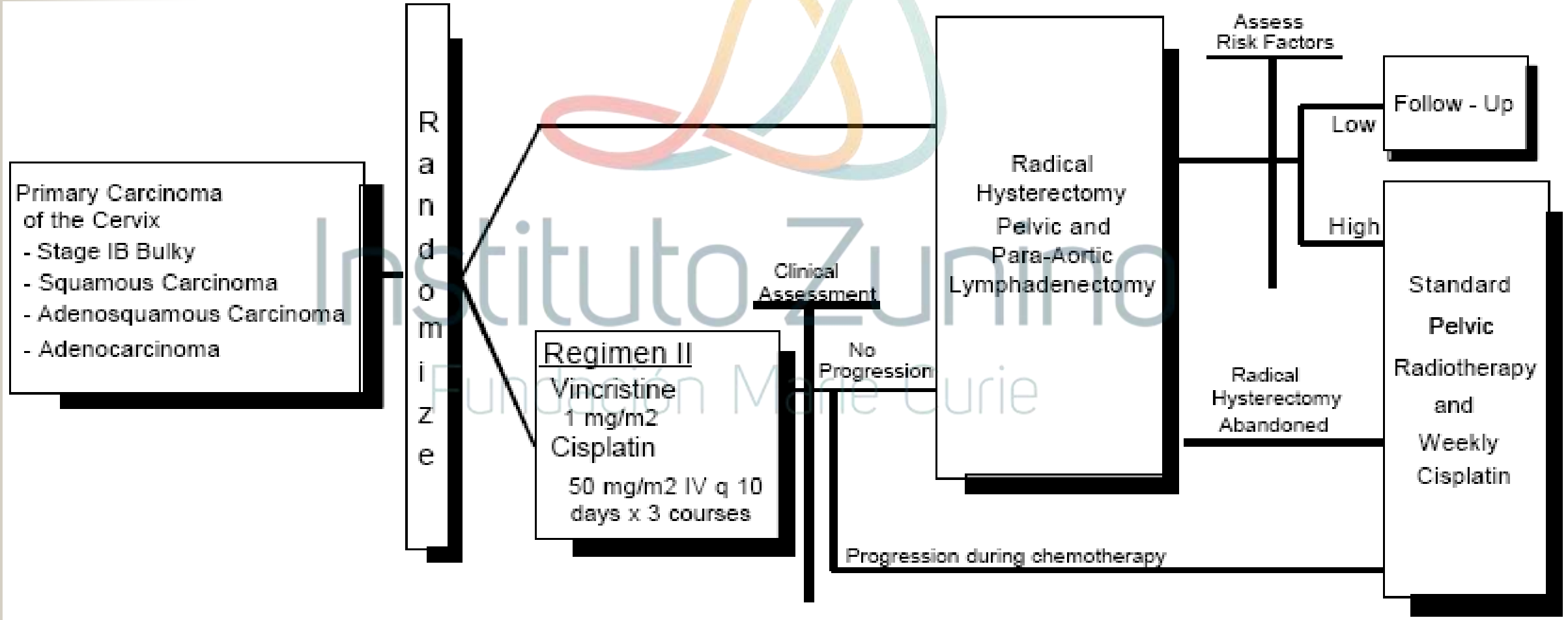
No diff. in PFS

NACt: **WORSE OS** in observational studies when compared with PST

NACt reduced the need of adj. RT by decreasing tumor size and (+) LNs, and distant metastasis

NACt failed to improve survival when compared with PST in patients with FIGO stage IB1 to IIA

Neoadjuvant Chemotherapy – GOG 141



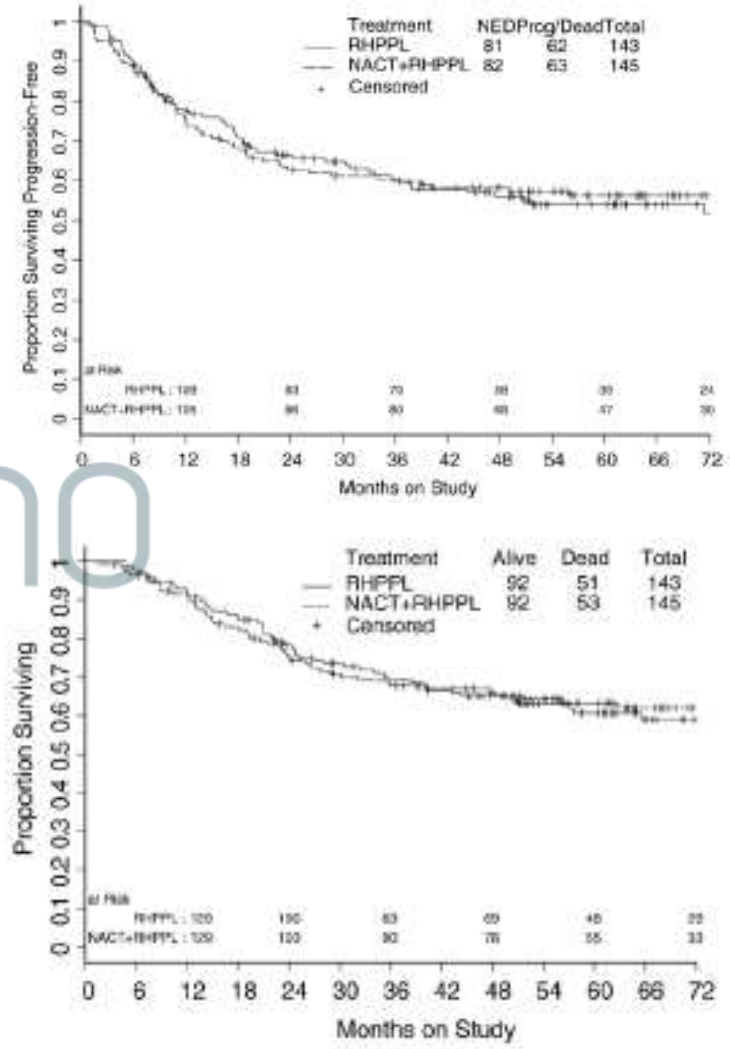
GOG -141. Eddy, GL et al. Gynecol Oncol 2007; 106: 362

288 pts enrolled - Closed after interim analysis showed study to be futile

Median FU, 62 months

- No difference between both groups in terms of need for adjuvant Tx: ~ 50%
- No difference in terms of surgical pathological risk factors at the time of the RH
- NACT did not increase operability rate: ~ 78%
- No improvement in survival when compared with GOG 92 & GOG 109 data
- Increased hematological, GI and neurological toxicity with NAcT

"Neoadjuvant CT should be considered unacceptable prior to Radical Hysterectomy" **- B. Monk, MD**



Locally or Locoregionally Advanced Cervical Cancer

NACt + RT or Surgery
vs
RT alone

NACt for LACC - Meta-analysis Collaboration
NACt followed by RT or Surgery vs RT

Eur J Cancer. 2003;39(17):2470

NACt followed by RT vs RT alone

- **18 trials, 2074 patients**
- No definitive conclusions could be made
- Substantial heterogeneity
  - Shorter cycle lengths and higher dose intensities of CDDP tended to show an advantage for NACT on survival

NACt followed by surgery vs RT alone

- **5 trials, 872 patients**
- **Reduction in the risk of death with NACt**
  14% improvement in 5-year OS, from 50%-64%
- Significant heterogeneity between trials
  - Timing and dose intensity of CDDP-based NACT appears to have an important impact on whether or not it benefits women with LACC

[Surgery + RT] vs [NACt (CDDP+VCR+Bleo) + Surgery + RT]

Sardi et al, Gynec Oncol, 1997; 67: 61

N=205 pts, IB >2cm [117 pts with bulky IB2]. FU 62 months

- S+RT = control group = 103 pts
- NACt + S + RT = experimental arm = 102 patients

Results: NACt was associated with

- Improved Survival and DFS in patients with bulky tumors (> 4 cm), related to increased resectability rate (100% vs 85%)
- Less histopathological High-risk features
- Decreased Pelvic failures

NACt + Surgery vs RT alone

Chang et al, JCO, 2000; 18: 1740

N= 124 pts, Bulky (>4cm) IB, IIA . Median FU = 39 months

- NACt (CDDP+VCR+Bleo) x 3 + RH (Type III) = 68 pts
- RT alone = 52 pts

Results

- No difference in overall survival or DFS
- Relapse Rate: **31% (NACt) vs 27% (RT)**
  - Besides the low dose of RT delivered [Median dose pt A 72 Gy]
  - Approximately **30 % of RH pts received adjuvant RT**

NACt + Rad Hyst and RT alone: similar efficacy for bulky St IB or IIA

NACt + Surgery vs RT

Benedeti-Panici, JCO, 2002:179-188

- 441 pts, stage IB2-III, randomized to CDDP-based NAcT + Type III-IV hysterectomy vs RT alone
  - PFS, P= 0.02
    - CT+S 55%
    - RT 41%
  - Overall survival, P= 0.007
    - CT+S 59%
    - RT 44.5%
- Conclusion: "Survival benefit to NAcT on subgroup analysis limited to IB2-IIB pts"

- Criticisms:
  - 28% Protocol violations
  - 22% Surgery abandoned
  - 30% Adjuvant RT
  - RT alone arm very poor outcome
    - Most of these pts should have received CT+RT
  - Poor quality RT in the control arm
    - Point A dose low (71 Gy) in RT alone
    - Median treatment time 62 days
    - 28% pts had Tx time longer than 100 days

Defining the Role of NACt + S vs RT in LACC
A Meta-analysis of Phase III Trials

M. A. Osman - J of Obst. and Gynecol. of India, 2016; 66:352–357

Inclusion criteria:
RCT, 2000-2012
FIGO St IB2-IVA

Primary Endpoint:
Survival

7 RCT - 1171 patients

- 5-year PFS: NACT-S, 62% vs RT, 45.5%
- 5-year OS: NACT-S, 66% vs RT, 49%
- 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.

Phase III: EORTC-55994

Closed to Accrual. Primary Endpoint OS

St IB2 and IIA (≥4 cm) and StIIB cervical cancer

Arm I

Cisplatin based NACt - q 21d

Type III-V Piver-Rutledge radical hysterectomy

Adjuvant EBRT +/- ICB if:
Positive lymph nodes and/or
Tumor invasion into the parametria and/or
< 5 mm margins

Arm II

Pelvic RT + weekly CDDP + ICBT

Adjuvant hysterectomy allowed in case of histologically proven residual tumor

Cervix Cancer. Treatment Scheme

EORTC
European Organisation for Research and Treatment of Cancer

N=686

Eligibility Check

Randomization

EORTC 55994

Arm 1: Neoadjuvant QT

Cisplatin based chemotherapy :
-min. cumulative cisplatin dose of 225 mg/m^2
-25 mg/m^2 per week,
-final dose no later than D64

Followed by surgery (radical hysterectomy)

Arm 2: concomitantly QT/RDT

Cumulative cisplatin dose 200-240 mg/m^2.
- Max 6 administrations.
- Dose 40 mg/m^2, max 80 mg

External radiotherapy (45-50 Gy) in fractions of 1.8 Gy to 2 Gy + external boost or brachytherapy
- min. 75 Gy EQD2 to point A (80 Gy to High Risk PTV) is mandatory
- overall treatment time ≤ 50 days

PIs: G. Kenter, S. Greggi, F. Landoni

Endpoints. EORTC 5594

Primary endpoint:

- Overall survival

Secondary endpoints:

- Progression free survival
- Toxicity
- Quality of life

686 Participants

Recruitment start: 20/12/2002 **Recruitment end:** 01/07/2014

NAC – Clinical Trials

Tata Memorial Hospital – Phase III trial. Primary Endpoint DFS

A Prospective Randomized Trial of NACT and Surgery Versus Concurrent CT+RT in Patients With Stage IB2-IIB

SCC - Uterine Cervix

ARM 1:
NACT followed by Surgery

NACT:
Taxol + Carbo
3 cycles

Radical Hysterectomy Class III + Bilateral PLND + Lower PA-LNS

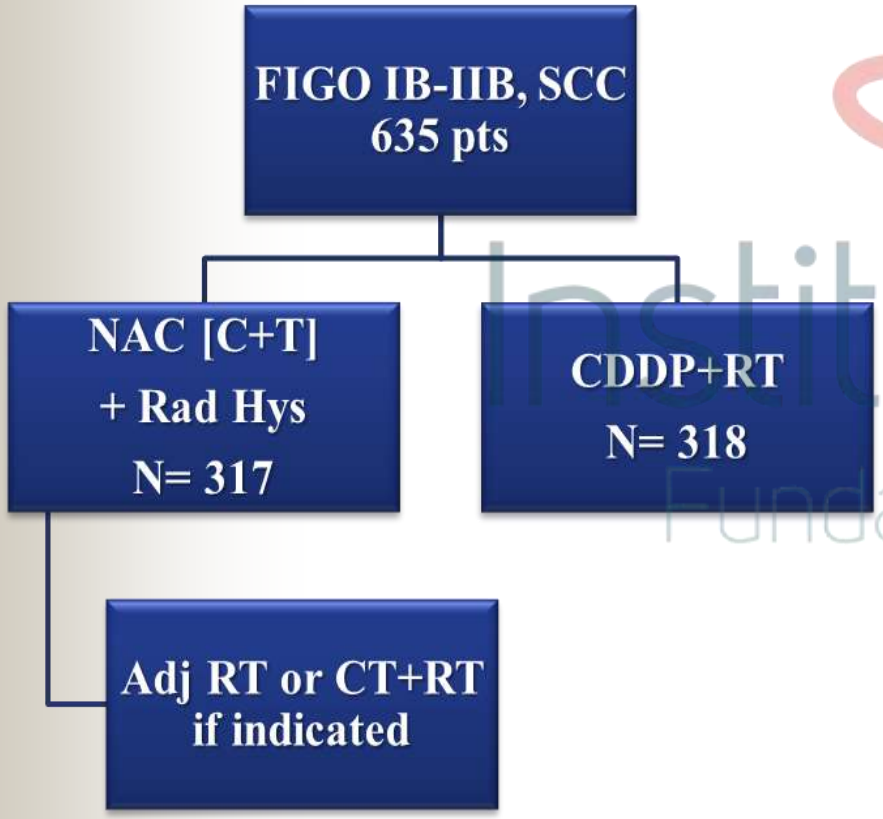
ARM 2:
Concurrent CT+RT

Pelvic RT + weekly Cisplatin

ICBT

NAC + Radical Surgery vs Concomitant CRT in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: RCT.

S. Gupta et al . J Clin Oncol. 2018; 1;36(16):1548-1555



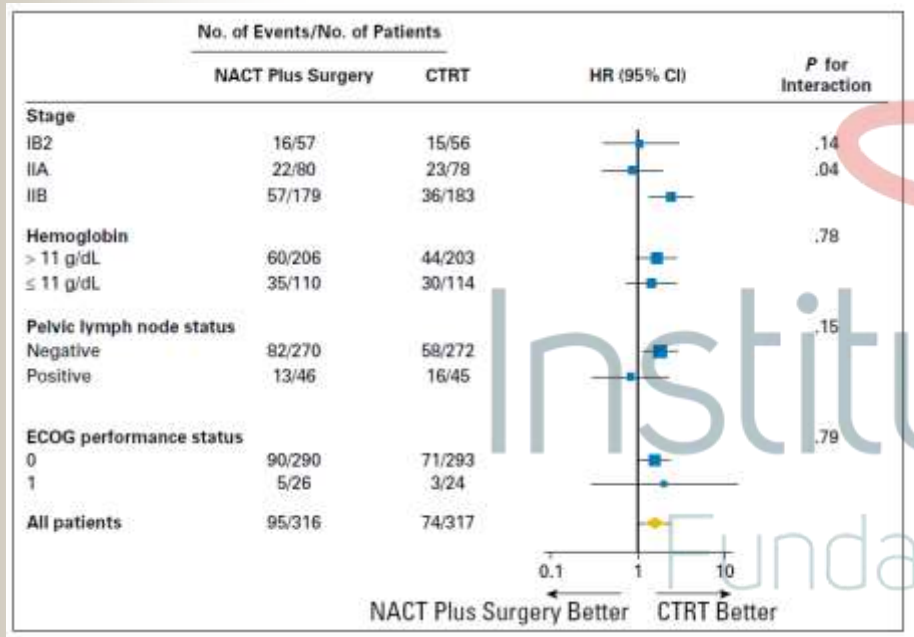
Endpoints: Primary = DFS; Secondary = OS & Toxicity.

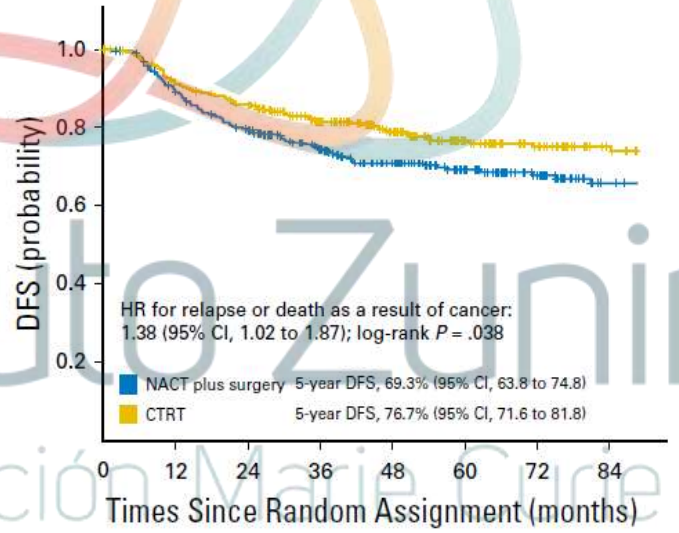
Median FU = 58.5 m

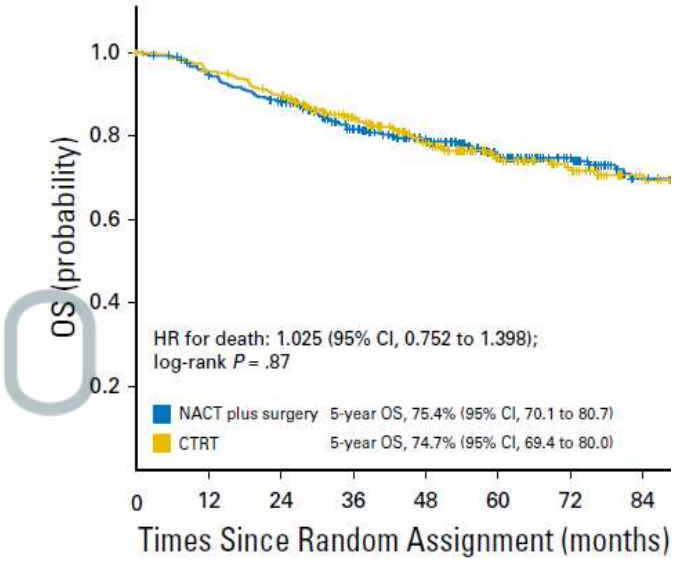
- **5-year DFS: NAC, 69% vs CRT, 77% [P = .038]**
- 5-year OS: NAT, 75% vs CRT, 75%
- ≥2 year (%) toxicities: NAC vs CRT
  - Rectal: 2.2% v 3.5%
  - Bladder:1.6% v 3.5%
  - Vaginal: 12.0% v 25.6%

Conclusion Cisplatin-based CRT resulted in superior DFS compared with NAC+S in LACC

Tata Memorial Hospital – Phase III trial







Locally or Locoregionally Advanced Cervical Cancer

NACt followed by Definitive CRT

A phase II study of weekly NAC followed by radical CRT for LACC

M McCormack et al. British Journal of Cancer (2013) 108, 2464–2469

Phase II trial: 46 pts, LACC (St IB2-IVA). SCC, 72%; ADC, 22% ; Adenosquamous, 7%

Dose-dense carboplatin (AUC2) and paclitaxel (80 mg/ m2) weekly X 6 cycles followed by Standard CRT

Primary Endpoint: RR @ 12 wks post-CRT. FIGO St IB2 (11%), II (50%), III (33%), IV (7%). FU 39 m

CR or PR: Post NAC, 70% ; Post CRT, 85%

3-years OS and PFS= 67% and 68%

Grade 3/4 toxicities: 20% during NACT and 52% during CRT

Conclusion: A good response rate is achieved by dose-dense weekly NACT (C+P)l followed by radical CRT. This treatment regimen is feasible as evidenced by the acceptable toxicity of NACT and by the high compliance to radiotherapy (98%).

ASCO-2018: NACt with cisplatin and gemcitabine followed by Standard CRT in LACC vs CRT: A phase III, prospective, randomized trial.

Silva S, et. al. J Clin Oncol 2018;36 suppl:5523.

107 pts with LACC

(FIGO IIB-IVA)

SCC (88%)

IIB (43%) or IIIB (45%)

Randomization:

NACt [Cisplatin 50 mg/m^2 D1 and Gemcitabine 1000mg/m^2 D1 and D8] x 3 cycles + Standard CRT

Vs

Standard CRT

Endpoints

Primary:

3-year PFS

Secondary:

RR, OS and toxicity

Median FU 25.5 m

3-year PFS: NACt 41% vs 60% CRT, p = 0.13

3-year OS: NACt 74% vs 82 CRT , p = 0.23

Complete RR:

54% NAC vs 82% CRT ,

p = 0.002

Overall RR: 93% NAC vs 94% CRT, p = 0.77

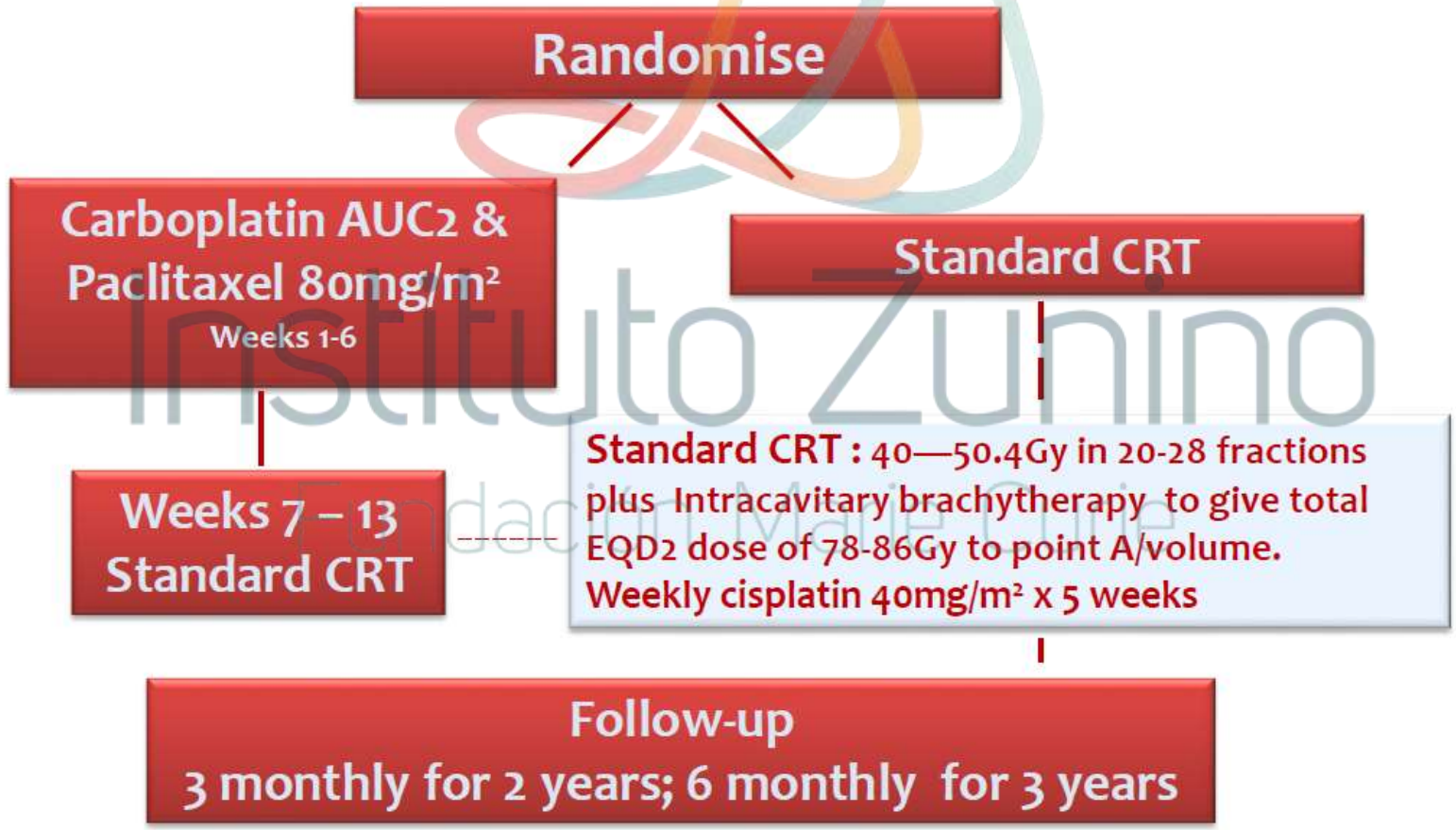
QoL improved after treatment in both groups

NAC is associated with inferior complete RR in comparison with standard CRT alone in the treatment of LACC

This is probably associated with the trend towards inferior PFS in NAC group

There was no statistically significant difference in OS

INTERLACE



INTERLACE

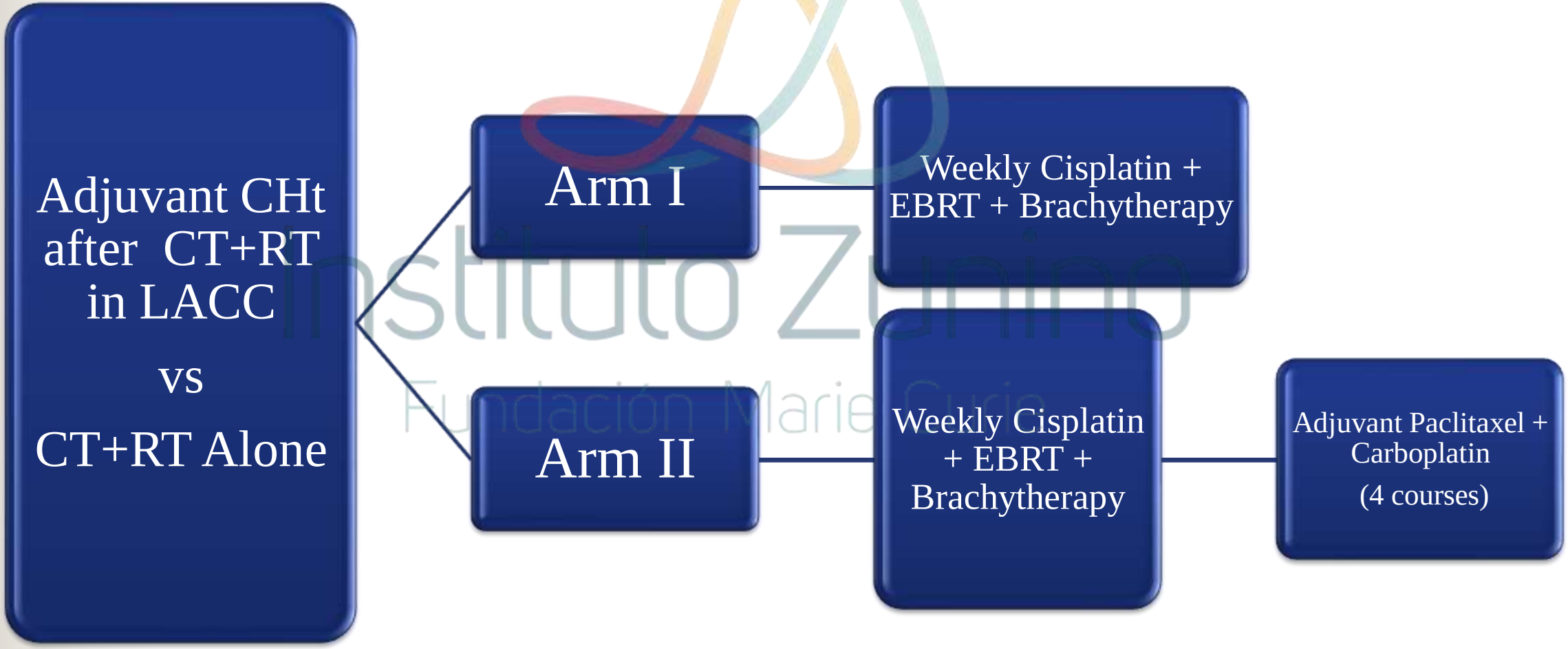
Eligibility criteria summary

- All patients suitable for CRT, FIGO IB1 with +ve nodes-IVA unless:
  - Nodes above aortic bifurcation
  - Disease involves lower third of vagina (FIGO IIIA)

IMRT permitted

The OUTBACK Trial: Phase III

Primary endpoint: Overall Survival



Locally or Locoregionally Advanced Cervical Cancer

NACt followed by Definitive CRT and Surgery

Neo-adjuvant Platinum-based Chemotherapy followed by CRT and Radical Surgery in LACC: A Phase II Study

G. Ferrandina. EJSO, 2018; 44: 1062

Primary Endpoint: pCR ≥ 50% pts

45 patients, FIGO Stage IB2-IVA: 25 (55.5%) St IIB; 9 (20%) St III

NAC (Carbo+Taxol) x 2, IMRT+SIB (TD=50.4 Gy, CTV1, 39.6 Gy, CTV2) – **No brachytherapy !!!!**

(+) LNs Pelvis: 38 pts (84.4%)

pCR: 18 / 40 pts (45%)

3-year PFS and OS: 66% and 86%, respectively

Conclusions: NACT followed by CT/RT by IMRT and RS, is feasible and safe; failure to achieve the primary endpoint has to be recognized; however, enrollment of a higher rate of poor prognosis patients compared to historical data used to calculate sample size, could have resulted in reduced activity.

Conclusions

There is not Level 1 evidence supporting the use of NACt followed by Surgery compared with CT+RT in the management of locally or loco-regionally advanced cervical cancer

The role of NACt followed by definitive RT or the role of adjuvant CT after definitive CT+RT is still to be defined

RT [external beam and brachytherapy] are an important component in the management of Locally and/or Loco-regionally Advanced Cervical Cancer

Need for access to RT units in the Low-income countries where the incidence of Cervical Cancer is higher in order to improve World-wide cure rates in patients with LACC


Gracias