Gynecologic Cancer InterGroup
Cervix Cancer Research Network

Review of Current CCRN Trials

William Small, Jr., M.D., FACRO, FACR, FASTRO
Professor and Chairman
Loyola University Medical Center

Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand

CCRN Trials

- TACO (KGOG/Thai)
- OUTBACK (ANZGOG)
- INTERLACE (NCRI)
- SHAPE (NCIC CTG)

> 60 accruals as of August 2015

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

KGOG Korean Gynecologic Oncology Group

ASGO Asian Society Of Gynecologic Oncology

Wellcome to TACO!

TACO

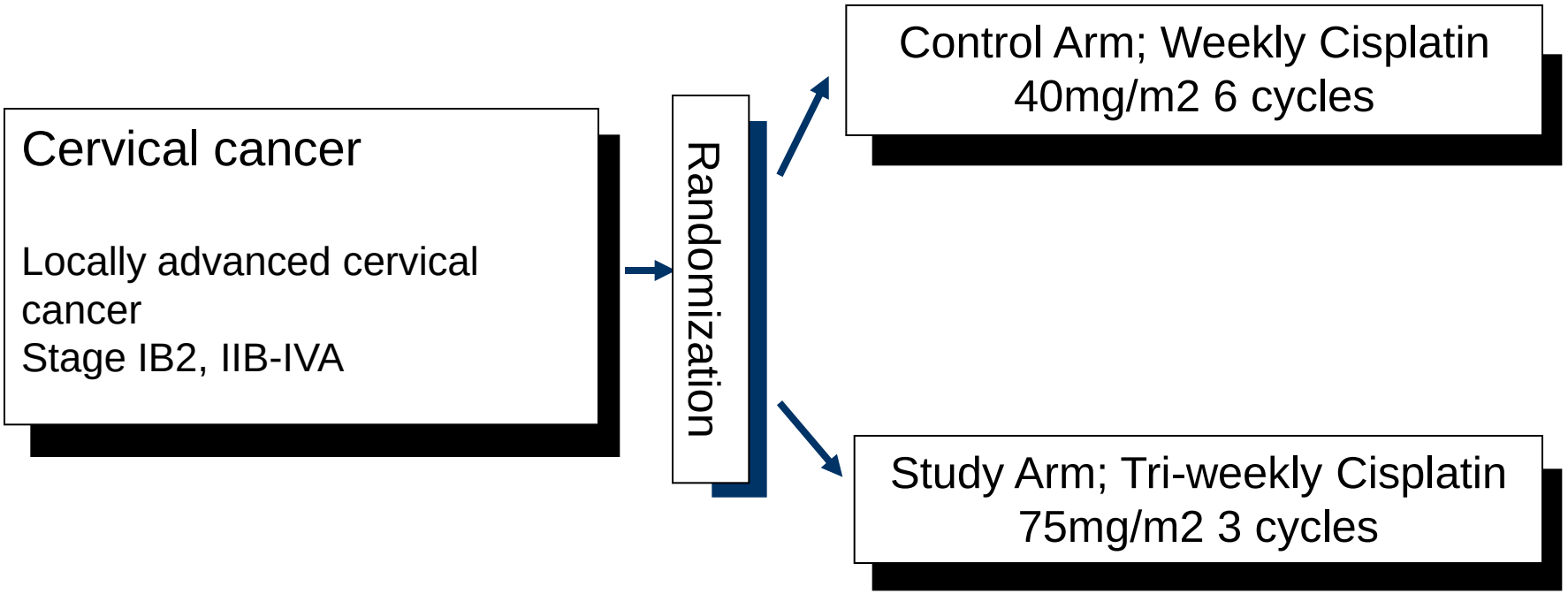
GCIG/KGOG1027/TGCS2012: Randomized Phase III Clinical Trial Comparing Weekly vs Tri-weekly Cisplatin Based Concurrent Chemoradiation in Locally Advanced Cervical Cancer

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)



Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

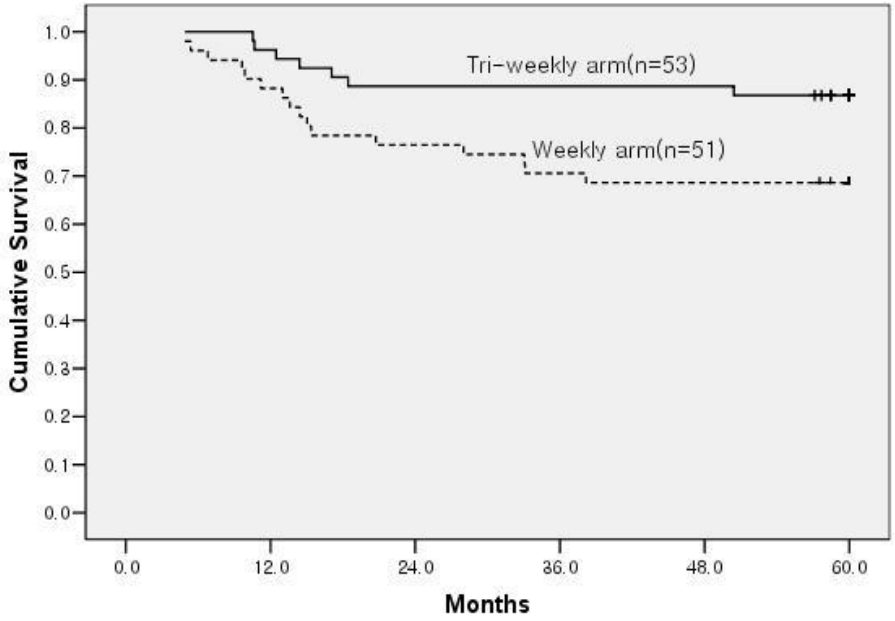
Weekly Cisplatin vs Tri-Weekly Cisplatin; Randomized phase II trial

- 2002-2004
- 105 patients
  - Stage IIB-IVA
    - Arm 1: Weekly cisplatin 40mg/m^2
    - Arm 2: Tri-weekly cisplatin 75mg/m^2
- Primary end point; compliance
  - Percentage of completed cycle
  - Toxicity

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

5-Year Complete Observation: Long term outcome



5YSR (n=105)

88% (Tri-weekly)
66% (Weekly)

HR 0.375 , 95% CI(0.154-0.914) , p=0.03

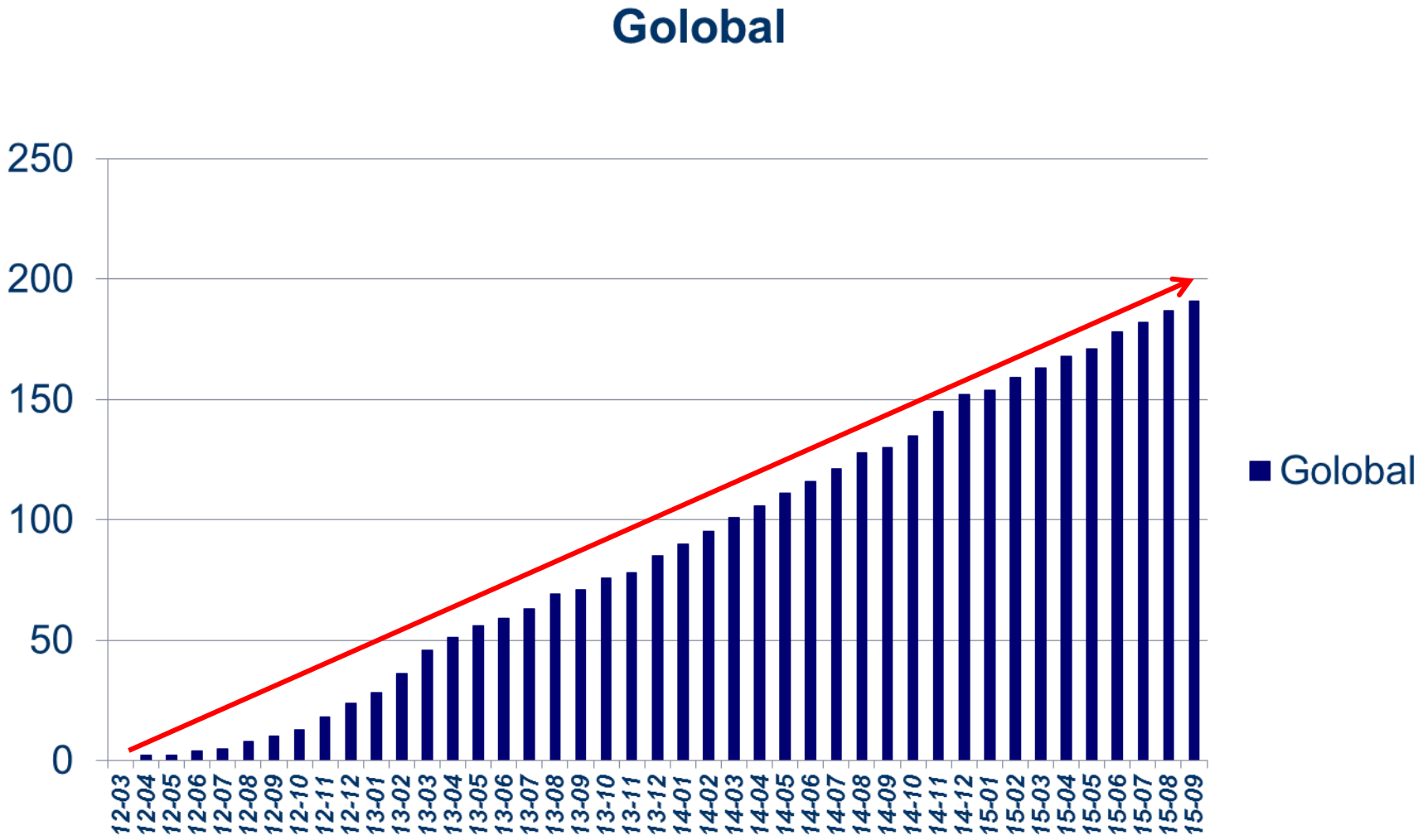
TACO: GCIG/KGOG1027

- Statistics
  - 10% increase of 5 YSR (65-> 75%)
  - 80% power, Two-sided test type I error=5%
    - Expected HR=1.50
  - 265/arm , 10% loss
  - Total; 590

TACO will prove…

- Hypothesis for Tri-weekly Cisplatin
  - Peak concentration of cisplatin may be more important.
    - To induced synergy of chemoradiation
    - To eliminate the micrometastasis

Accrual of TACO 2015.09.30



Gynecologic Cancer InterGroup
Cervix Cancer Research Network

THE OUTBACK TRIAL

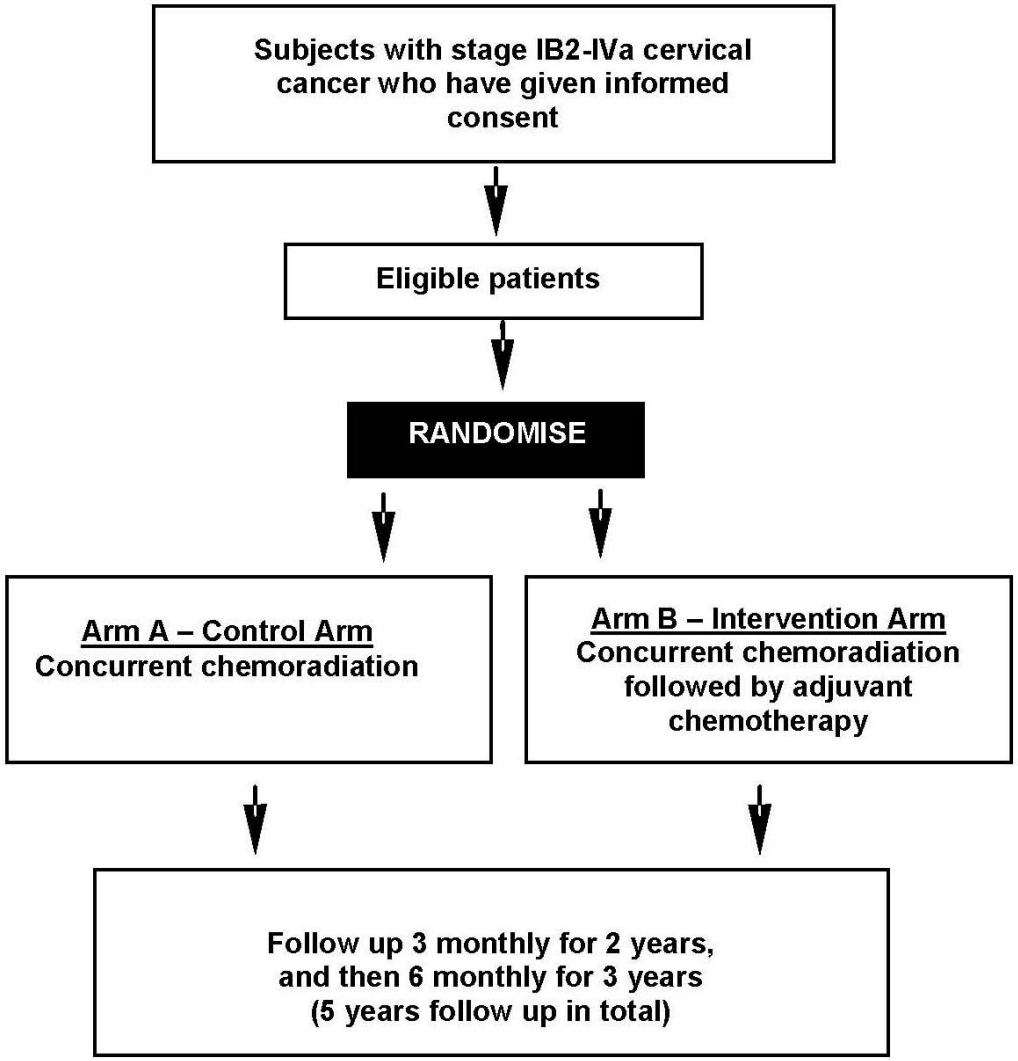
A Phase III trial of adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone

Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand

Background

- Concurrent cisplatin and radiation the standard of care for locally advanced disease for some time
- Meta-analysis showed 6% improvement in 5 year overall survival rate with the addition of concurrent chemotherapy (60 to 66%)
- 5 year disease free survival rate (50 to 58%) still leaves much room for improvement with most women dying from metastatic disease

Design: International randomized phase III



Inclusion criteria

Stage $1B_2$-IVa cervical cancer suitable for primary treatment with chemo-radiation with curative intent in addition to:

- ECOG performance status 0-2
- Histological diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma
- WBC ≥ 3.0 x 10^9/L and ANC ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Bilirubin ≤ 1.5 x UNL

Objectives

- **Primary objective:** To determine if the addition of adjuvant chemotherapy to standard chemoXRT improves progression-free survival
- **Secondary objectives:** To determine
- Overall survival rates
- Acute and long-term toxicities
- Patterns of disease recurrence
- The association between RT compliance and outcomes
- Patient QOL, including psycho-sexual health

Radiotherapy

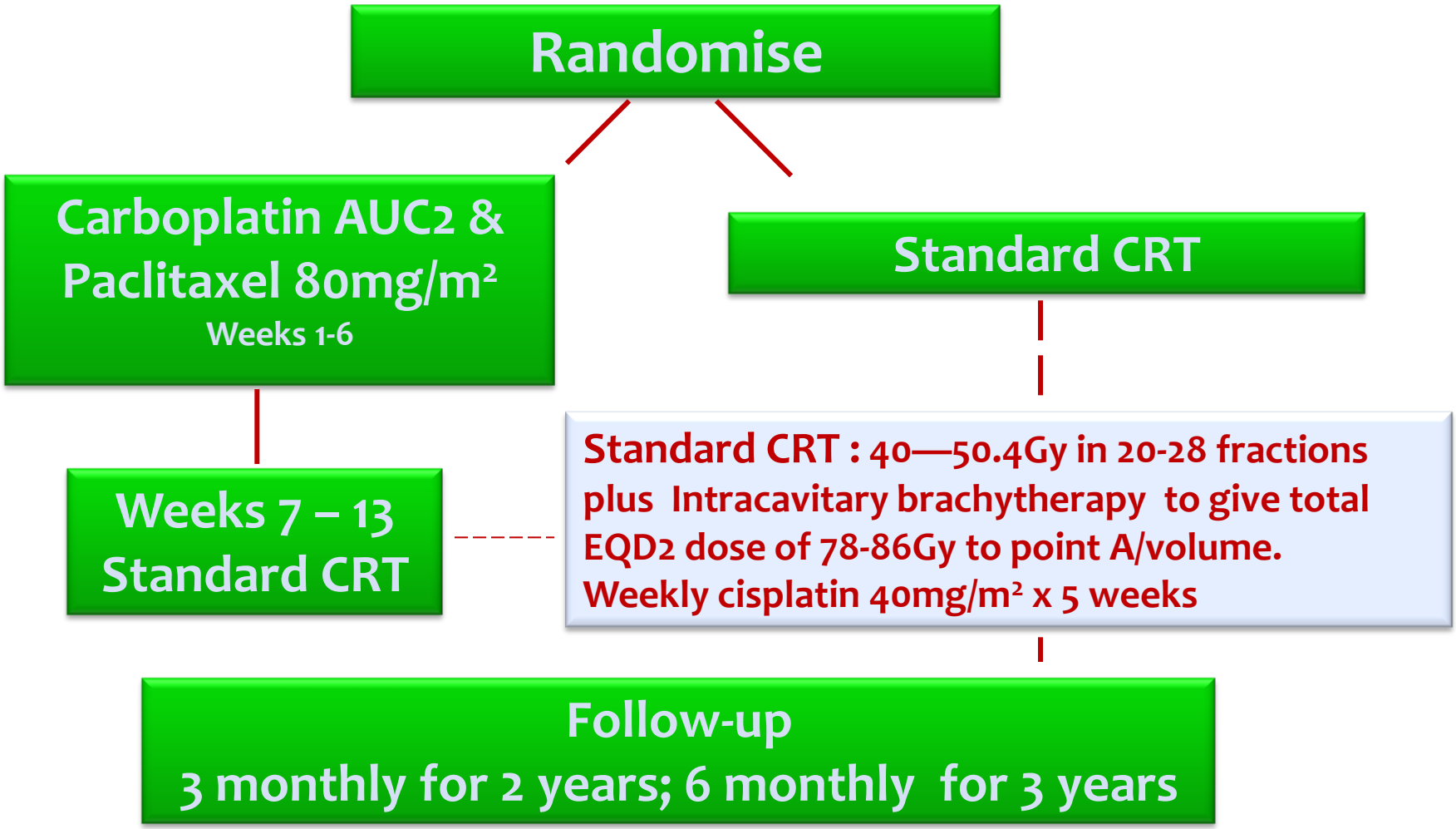
- 40-50.4 Gy of external beam XRT in 1.8 – 2.0 Gy fractions plus brachytherapy and a boost to involved nodes
- Parametrial boost is allowed but not mandatory
- Total dose to nodal boost range of 46 Gy (2.0 Gy/fx) to 68 Gy (1.8 Gy/fx).
- Brachytherapy: LDR or HDR
- The primary tumour should receive a total dose of 80 – 90 Gy from EBRT plus brachytherapy

OUTBACK (ANZGOG0902/GOG 0274 / RTOG 1174)

A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone.

Current accrual (9 Oct 2015)								
	Aust	NZ	USA	Canada	Saudi Arabia	Singapore	CCRN	**TOTAL**
No. of Sites open	12	3	238	5	1	1	0	**260**
No. of patients	116	13	488	20	5	1	0	**643**

INTERLACE


Randomise
Carboplatin AUC2 & Paclitaxel 80mg/m²
Weeks 1-6
Standard CRT
Weeks 7 – 13 Standard CRT
Standard CRT : 40—50.4Gy in 20-28 fractions plus Intracavitary brachytherapy to give total EQD2 dose of 78-86Gy to point A/volume. Weekly cisplatin 40mg/m² x 5 weeks
Follow-up
3 monthly for 2 years; 6 monthly for 3 years

Induction Chemotherapy

Paclitaxel and carboplatin - weekly treatment for six weeks

Week	1	2	3	4	5	6
	Mon, Tues or Wed	**Mon, Tues or Wed**	**Mon, Tues or Wed**	**Mon, Tues or Wed**	**Mon, Tues or Wed**	**Mon, Tues or Wed**
Carboplatin AUC2	•	•	•	•	•	•
Paclitaxel 80mg/m²	•	•	•	•	•	•

Chemoradiation

Cisplatin weekly treatment for five weeks

Week	7	8	9	10	11	12
Days	1-5	8-12	15-19	22-26	29-33	36-40
Radiotherapy: 40-50.4Gy in 20-28 fractions	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ●
Cisplatin 40mg/m² Mon, Tues or Wed	●	●	●	●	●	

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Stratification

- FIGO stage
- Node status – positive / negative
- Tumour Volume
- Squamous vs. non-squamous
- IMRT vs. no IMRT
- Age
- Recruiting site

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

Current status

- 27 sites (UK) open to recruitment (6 in set-up)
- 83 patients recruited (Target recruitment – 770)

<u>INTERNATIONAL</u>

- GICOM (Mexico) – INCAN
- MaNGO (Italy) – 3 sites in setup

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

the **SHAPE** Trial:
Simple **H**ysterectomy **A**nd **P**elvic node dissection in **E**arly cervix cancer

Comparing radical hysterectomy and pelvic node dissection against simple hysterectomy and pelvic node dissection in patients with low risk cervical cancer

Chair: Marie Plante
University of Laval, Quebec City

An NCIC Clinical Trials Group proposal for the Gynecological Cancer Inter Group (GCIG)

Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand

the SHAPE trial: Background

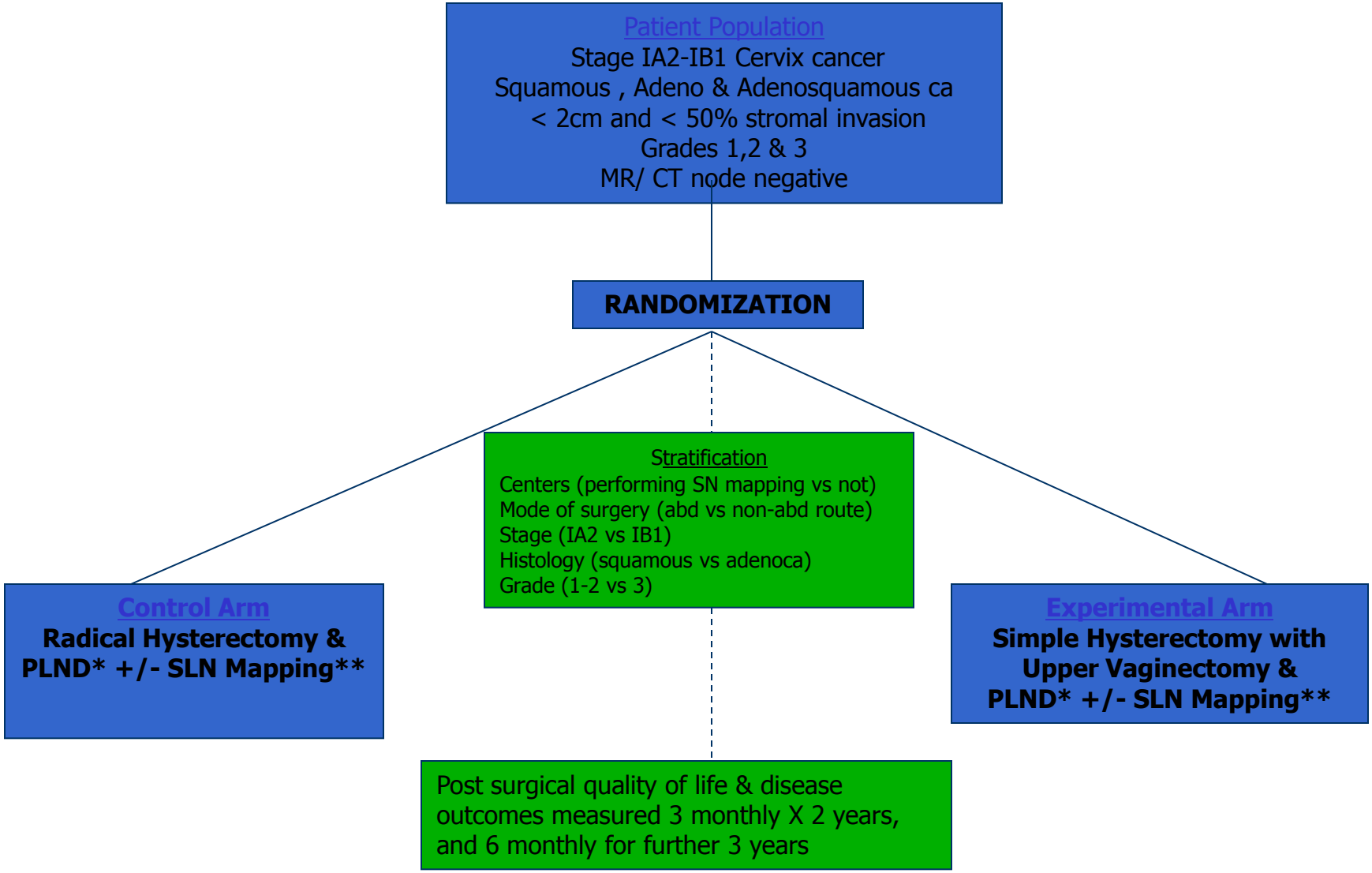
- Radical Hysterectomy plus pelvic node dissection (RPHN) is regarded as the standard treatment for young, early cervix cancer patients with tumors smaller than 4cm. More than 85% of patients treated surgically are free of disease at 5 years

- The pelvic relapse of operable early cervix cancer patients is most associated with: pelvic lymph node involvement, large tumours, deep invasion and paracervical disease. Detection of combinations of these features results in the need for post operative adjuvant therapy, the benefit of which is well documented by trials in high risk (Peters, JCO 2000) and intermediate risk situations (Sedlis, NEJM 1999)

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

the SHAPE trial: Side effects

- Between 20-30% of patients undergoing RHPN experience serious immediate or longer term effects:
  - Acute complications include: Urinary, rectal, ureteric dysfunction (5%), Lymphedema (7%), lymphocyst (20%), nerve damage (2%) and general issues such as wound dehiscence and DVT
  - Longer term effects include: Bladder dysfunction, sexual difficulties, ovarian damage and pelvic muscle damage (5-10%)
- These result in long term impact on quality of life and sexual health


Patient Population
Stage IA2-IB1 Cervix cancer
Squamous , Adeno & Adenosquamous ca
< 2cm and < 50% stromal invasion
Grades 1,2 & 3
MR/ CT node negative
RANDOMIZATION
Stratification
Centers (performing SN mapping vs not)
Mode of surgery (abd vs non-abd route)
Stage (IA2 vs IB1)
Histology (squamous vs adenoca)
Grade (1-2 vs 3)
Control Arm
Radical Hysterectomy & PLND* +/- SLN Mapping**
Experimental Arm
Simple Hysterectomy with Upper Vaginectomy & PLND* +/- SLN Mapping**
Post surgical quality of life & disease outcomes measured 3 monthly X 2 years, and 6 monthly for further 3 years
* PLND – Pelvic lymph node dissection
**SLN - Sentinel lymph node mapping optional

the SHAPE Trial: Its goal

- To show that simple hysterectomy in low risk cervix cancer patients is safe and is associated with less morbidity than radical surgery:
  - AND that overall survival will not be significantly different for RHPND or SHPND, even if a slightly higher relapse rate occurs in the latter group

Primary endpoint

- Compare the 3-year pelvic recurrence rate between radical and simple hysterectomy patients

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

the SHAPE trial: Patient Population

Inclusion criteria

-Stage IA2-IB1< 2cm cervix cancer pts

- < 50% stromal invasion (MRI) or <1cm depth of invasion on LEEP/cone

-Squamous, adeno OR adenosquamous

-Grade 1, 2, 3

-LVSI allowed

-Radiologically node negative - MRI or CT

Exclusion criteria

-High risk histology
clear cell, small cell

-Stage IA1

-Neoadjuvant chemotherapy

-Pregnancy

-Desire to preserve fertility

the SHAPE trial: Adjuvant treatment guidelines

- If high or intermediate risk features are identified on final pathology patients will be considered for adjuvant treatment, according to NCIC guidelines:

<u>High Risk defined as</u>

- positive nodes
- positive parametria
- positive surgical margins

<u>Intermediate Risk defined as having 2 of following three criteria</u>

- tumours bigger than 4cm (on final pathology)
- deep stromal invasion (greater than 66%)
- lymphvascular invasion

SHAPE Oct 2015

RADICAL HYSTERECTOMY AND PELVIC NODE DISSECTION VS SIMPLE HYSTERECTOMY AND PELVIC NODE DISSECTION IN PATIENTS WITH LOW-RISK, EARLY- STAGE CERVICAL CANCER

Country	# Patients Accrued
Austria	5
Belgium	4
Canada	68
China	2
France	7
Ireland	4
South Korea	7
The Netherlands	5
United Kingdom	1
Total	**103**

SHAPE/CX.5 Sites Active as of Oct 5, 2015

Country	# Sites Activated
Austria	7
Belgium	5
Canada	17
China	1
France	15
Ireland	1
South Korea	1
The Netherlands	1
United Kingdom	8
Total	**56**

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

QUESTIONS?