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ESMO SUMMIT AFRICA

Current Management of Cervical Cancer

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PRESENTER DISCLOSURES

Advisory Board

Clovis Oncology

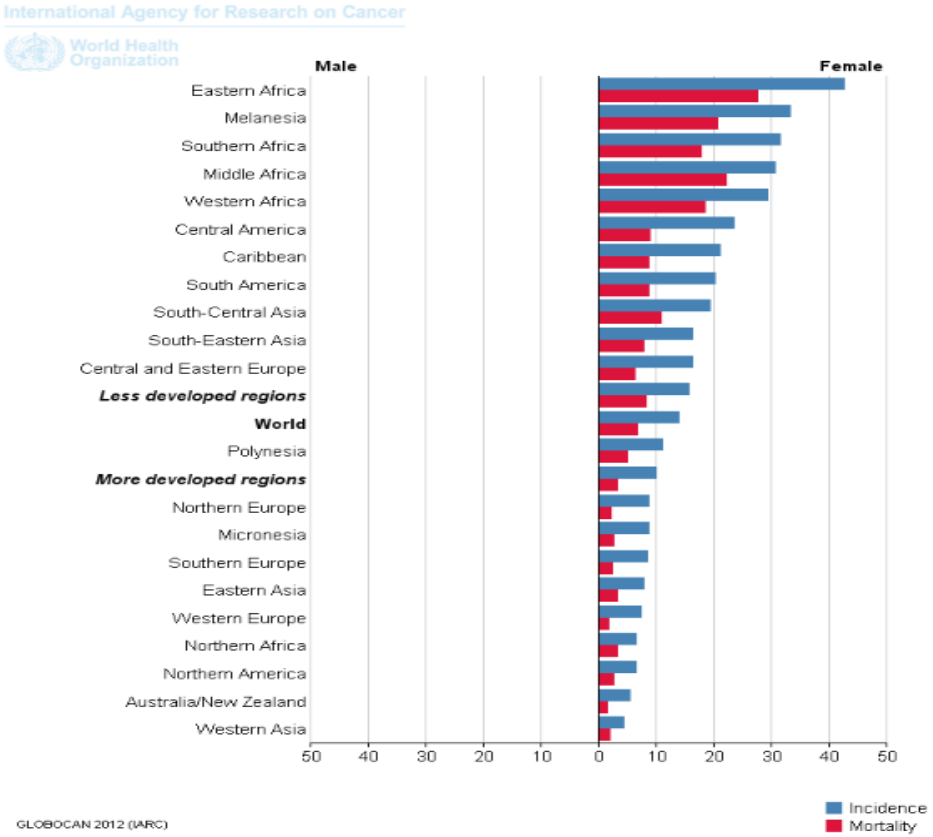
Novocure

Debiopharma

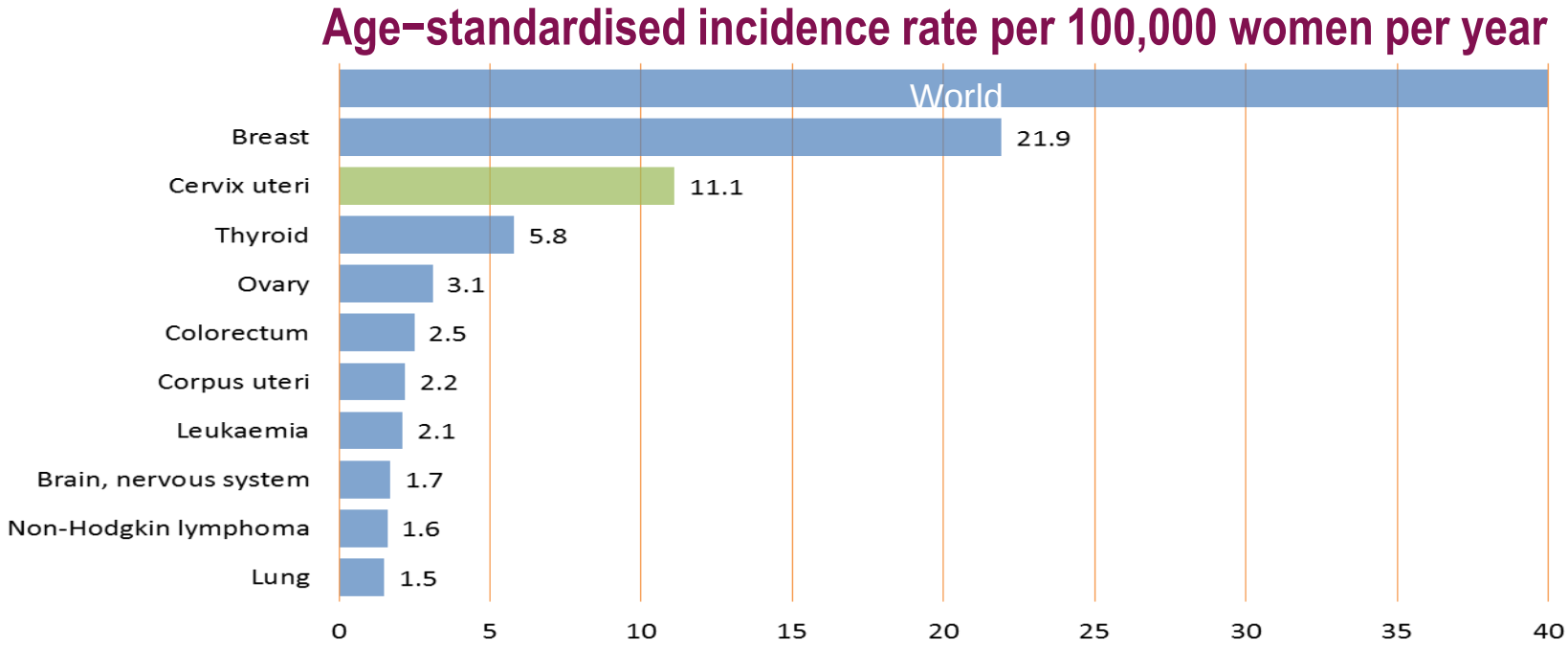
Study Grants

Pfizer

Cervical Cancer
Estimated Incidence, Mortality and Prevalence Worldwide in 2012



Cervical cancer is the 2nd most frequent cancer in women aged 15–44 years



GLOBOCAN 2012.

Cervical Cancer

- Third most common cause of female mortality
- Incidence 13.2/100’000 women/yr Europe
- Mortality 5.9/100’000/yr
- Incidence and mortality higher in developing countries (85% of cases, 90% of deaths)

Main risk factor	High risk HPV persistent infection
Additional risk factors	Immunosuppression Long term use of OC High parity Tobacco smoking

Diagnosis

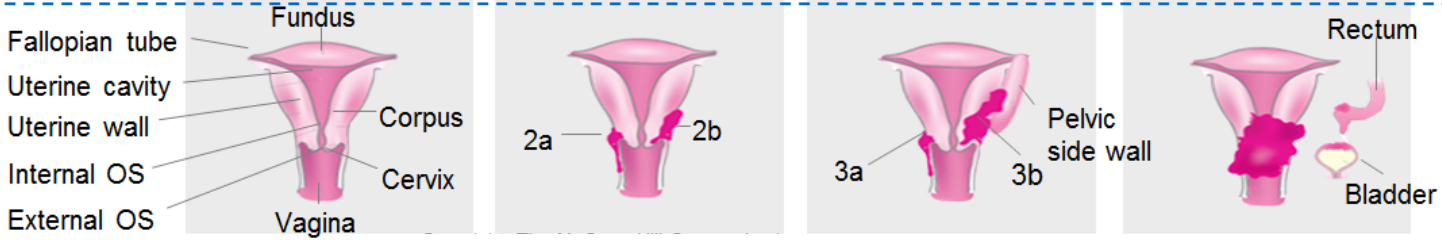
- Bimanual P/V examination, colposcopy, biopsy and/or endocervical currettage (ECC)
- MRI : to determine tumor size, degree of stromal penetration, vaginal and corpus extension.
- CT: to detect pathologic lymphnodes
- Chest xray
- Cystoscopy, rectoscopy (stages IIB-IV)

Staging and prognostic factors

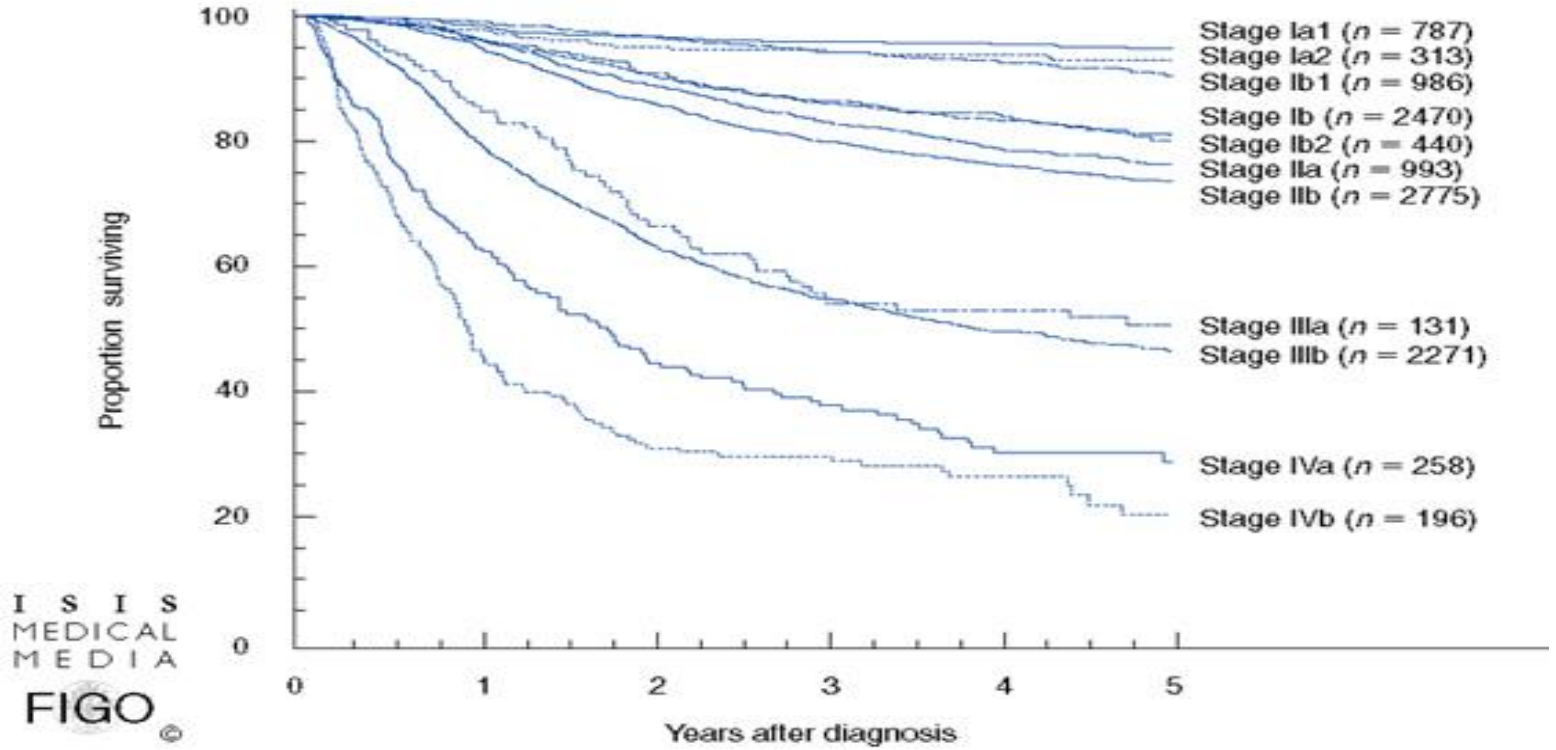
- FIGO staging on clinical examination: to select and evaluate therapy
- TNM staging on pathological findings: to estimate prognosis and compare results
- Prognostic factors: stage, tumor size, stromal invasion, nodal involvement, lymphovascular space invasion, histotype and differentiation.

FIGO Staging is based on the extent of tumor lesion

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Extent of tumour	Carcinoma in situ	Confined to cervix	Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina	Disease to pelvic wall or lower 1/3 of vagina	Invades bladder, rectum or metastasis
Stage at presentation		47%	28%	21%	4%



Survival by FIGO stage



WHO histological classification of cervical cancer

Epithelial tumors

Squamous tumors and precursors

Glandular tumors and precursors

- Adenocarcinoma

Other epithelial tumors

- Adenosquamous carcinoma

Neuroendocrine tumors

- Carcinoid

Mesenchymal tumors and tumor-like conditions

- Mixed epithelial and mesenchymal tumors

Primary treatment of cervical cancer

Consists of surgery followed by radiotherapy (RT) or concurrent chemoradiotherapy (CRT) depending on disease stage.

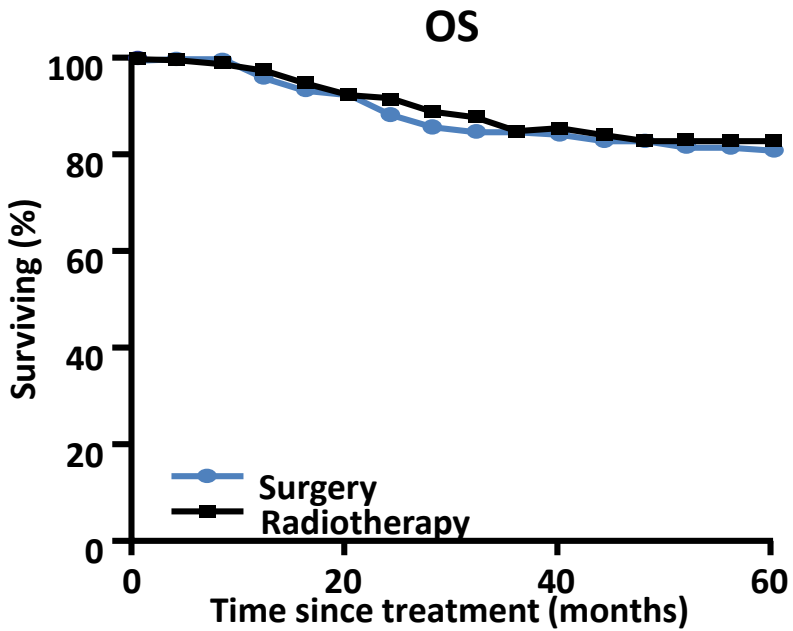
Definitive RT should consist of pelvic external beam radiation with high-energy photons and intracavitary brachytherapy administered at high doses (> 80-90 Gy) and in a short time (< 55 days)

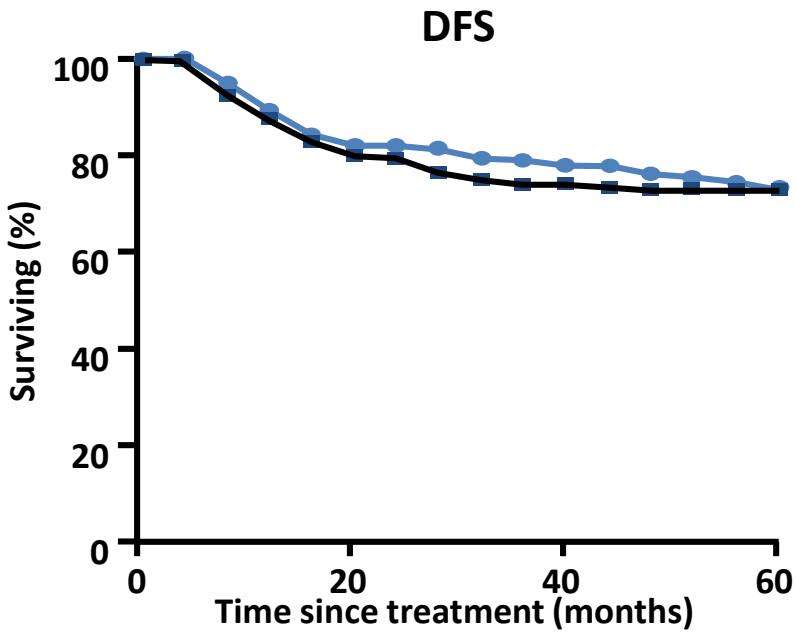
Early invasive cervical cancer

NIH Consensus Statement on Cervical Cancer
Bethesda 1996

“Patients with stage IB and IIA cervical cancer are appropriately treated with either radical hysterectomy with pelvic lymphadenectomy or radiation therapy with equivalent result.
To minimize morbidity, primary therapy should avoid the routine use of both radical surgery and radiation therapy.
The combined use of radical surgery and radical radiation therapy results in high morbidity and cost.”

Radical hysterectomy vs radiotherapy in patients with stage Ib cervical cancer





5-year OS (83%) and DFS (74%) did not differ significantly between the two groups

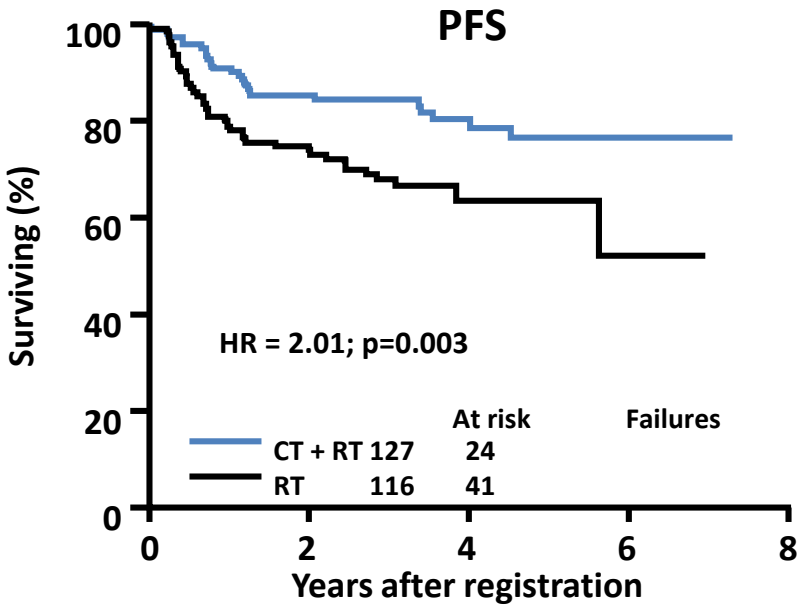
- DFS = disease-free survival; OS = overall survival

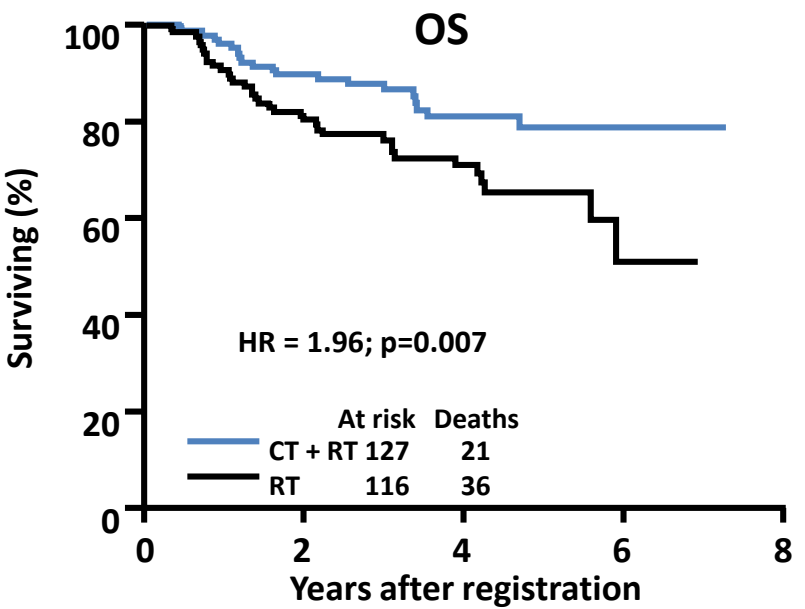
- Landoni, et al. Lancet 1997

Radical histerectomy vs radiotherapy in patient with stage IB cervical cancer

Morbidity	Surgery		Radiotherapy group (N=167)
	Surgery only (N=62)	Surgery plus RT (N=108)	
Grade 2-3 (%)	31	27	11
Short-term (%)	19		7
Long-term (%)	27		16

Concurrent chemotherapy + pelvic radiation therapy vs pelvic radiation therapy alone





The addition of concurrent cisplatin-based chemotherapy to radiation therapy significantly improves PFS and OS for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix

CT = chemotherapy; RT = radiotherapy

Peters et al. J Clin Oncol 2000

Radical surgery versus radiotherapy for stage IB-IIA cervical cancer

Optimum treatment strategy

Depends on:

- Prognostic factors
- Benefit and disadvantages of each treatment

Surgery	Radiotherapy
Younger patients Radiotherapy feasible in pelvic recurrence Information on nodal status	Obese, elderly patients Concomitant severe illness Salvage surgery in pelvic recurrence highly risky Delayed complications (mainly after combined approach)

2/22/99: NCI alert on cervical cancer

The results of 5 large studies have shown that women with invasive cervical cancer have better survival when they receive chemotherapy which includes the ***drug cisplatin along with radiation therapy.***

Concurrent chemoradiotherapy for cervical cancer: a meta-analysis of 18 randomized trials

- Greater effect for stage IB2-IIA/IIB
- Better results for platinum based therapy
- Greater benefit in overall survival with additional adjuvant CT

Meta-Analysis Group, JCO, 2008

ESMO Clinical Practice Guidelines

Stage	Treatment	
IB1, IIA	TAHBSO + PLND (IA)	Complementary CT/RT If risk factors (G3, LVSI, positive resection margins multiple nodes)
IB2	Concurrent CT/RT * with cisplatin ** (IA)	
II B - IV	Concurrent CT/RT with cisplatin (IB)	

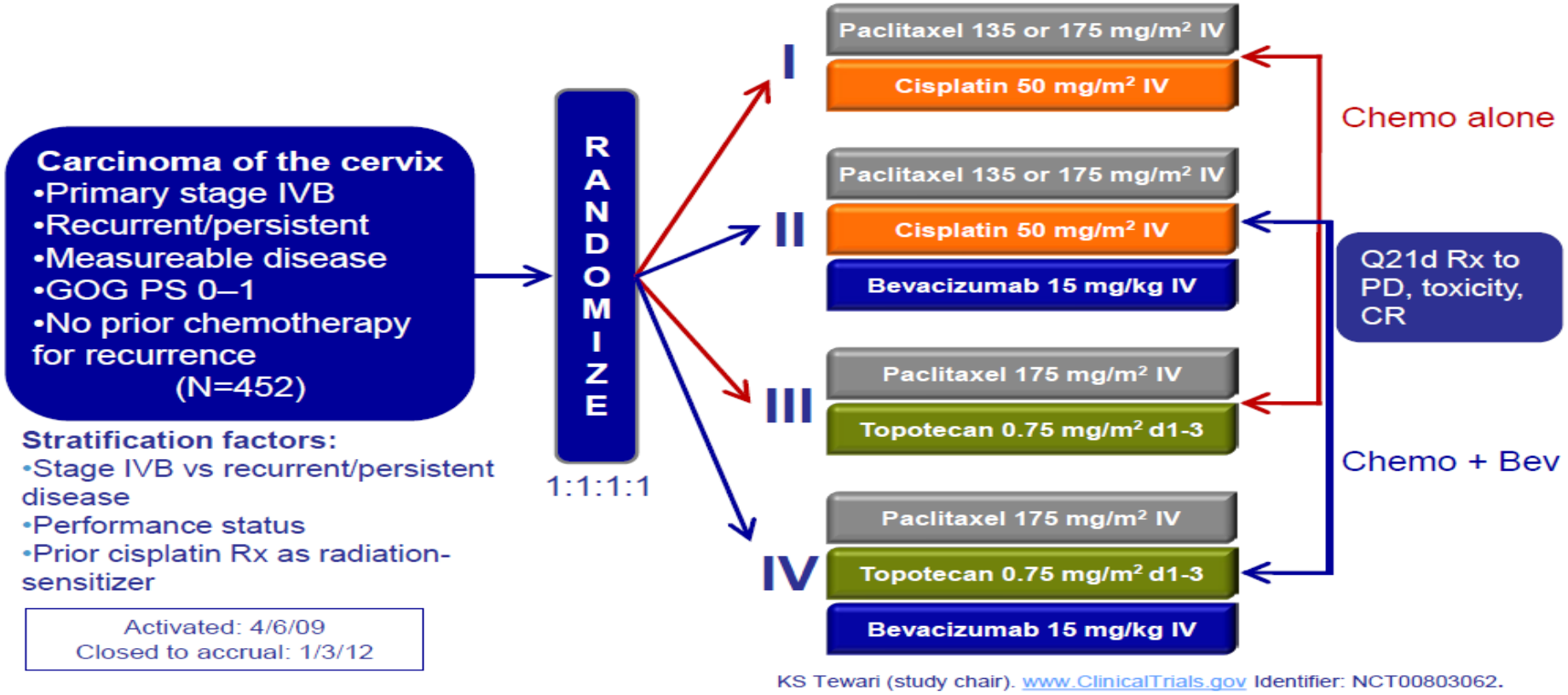
- RT: external beam radiotherapy + brachytherapy
- ** Cisplatin: 40 mg/ m^2/wk

Phase III trials of cisplatin doublets in stage IV B, recurrent or persistent cervical cancer

	Pts	Prior RT (%)	OR (%)	Gr 3/4 Neutropenia (%)	Median PFS (mo)
Cisplatin-paclitaxel	103	68	29	78	12.8
Cisplatin-topotecan	111	73	23	83	10.25
Cisplatin-gemcitabine	112	64	22	42	10.28

Only cisplatin radiosensitizer as prior chemotherapy

Phase III trial of bevacizumab in advanced cervical cancer (GOG study 240)

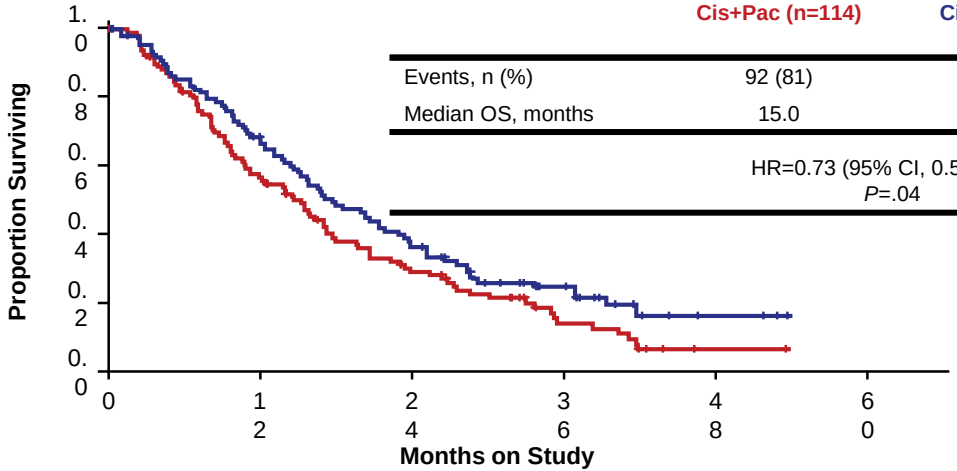


KS Tewari (study chair). www.ClinicalTrials.gov Identifier: NCT00803062.

GOG 240 : Demographics & Baseline Characteristics

Characteristic	Chemo Alone (n=225), %	Chemo + Bev (n=227), %
Median age, years (range)	46 (20–83)	48 (22–85)
Histology, % Squamous AdenoCa, unspec.	 68 20	 70 19
Race, % White African American Asian Pacific Islander	 80 11 3 0	 75 16 5 0
Stage of disease, % Recurrent Persistent Advanced	 73 10 16	 70 12 17
Performance status, % 0 1	 58 42	 58 42
Prior platinum, %	74	75
Pelvic disease, %	53	54

GOG 240 : final protocol-specified Overall survival Cisplatin-Paclitaxel versus Cisplatin-Paclitaxel-Bevacizumab



bev, bevacizumab; CI, confidence interval; cis, cisplatin; HR, hazard ratio; OS, overall survival; pac, paclitaxel.

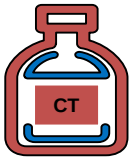
Tewari et al ESMO Madrid 2014

Bevacizumab in advanced cervical cancer
Updated Toxicity

Adverse Event, n (%)	Chemo Alone (n=220)	Chemo + Bev (n=220)
Treatment cycles, median (range)	6	7
Grade 5 AE(s)	3 (1.3)	7 (3.2)
GI events, non-fistula (grade ≥2)	97 (44)	115 (53)
GI fistula (grade ≥2)	1 (0.5)	11 (5)
GI perforation (grade ≥3)	0 (0)	5 (2.3)
GU fistula (grade ≥2)	1 (0.5)	8 (3.6)
Hypertension (grade ≥2)	4 (1.8)	55 (25)
Proteinuria (grade ≥3)	0 (0)	5 (2.3)
Pain (grade ≥2)	63 (29)	72 (33)
Neutropenia (grade ≥4)	58 (26)	80 (36)
Febrile neutropenia (grade ≥3)	12 (5.5)	12 (5.5)
Thromboembolism (grade ≥3)	4 (1.8)	18 (8.2)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade ≥3)	1 (0.5)	4 (1.8)
GU (grade ≥3)	1 (0.5)	6 (2.7)

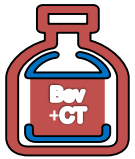
bev, bevacizuamb; chemo, chemotherapy; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary.

GOG 240: Bevacizumab Increased the Risk of Vaginal Fistulae



222 patients

GI-vaginal fistula: 2 patients (0.9%)
GU-vaginal fistula: 3 patients (1.4%)



218 patients

GI-vaginal fistula: 18 patients (8.2%)
GU-vaginal fistula: 4 patients (1.8%)
GI fistula: 1 patient (0.5%)

In a separate analysis of the GOG 240 study, all fistulae events were re-graded, and the results showed that:

- None of the fistulae were associated with peritonitis, sepsis or death. Among the patients who developed GI-vaginal fistulae, all (100%) had received prior pelvic radiation therapy compared to 80% in the overall population.

CT, chemotherapy; GI, gastrointestinal; GU, genitourinary

Willmott L et al. IGCS 2014 [abstract]

Bevacizumab in advanced cervical cancer

Conclusions

- The benefit conferred by the incorporation of bevacizumab is sustained beyond 50 months
- Key points
  - Significant improvements in OS, PFS, and response rate without significant deterioration in HRQoL
  - Bevacizumab is active also in the irradiated field
- Open issues
  - Generalizability of the results
  - Cost-effectiveness analysis missing

Randomised trial comparing cisplatin/paclitaxel with carboplatin /paclitaxel: a non inferiority study (JCOG 0505)

Stage IV B, persistent or recurrent cervical cancer, not amenable to curative surgery radiotherapy

Balancing factors:
Tumors outside of the prior irradiation field (yes or no)
PS 0-1 or 2
SCC or non SCC
Institution

RANDOMIZE

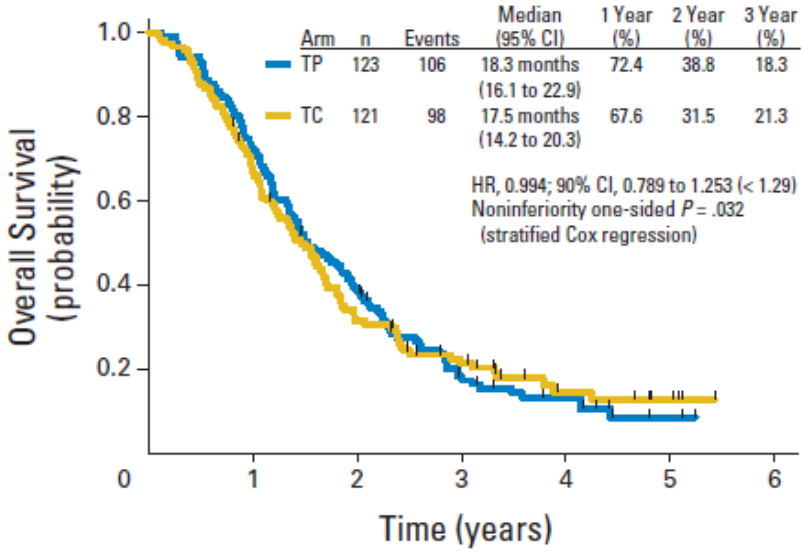
Standard: TP
Paclitaxel 135 mg/m^2 24h d1
Cisplatin 50 mg/m^2 d2

Every 21 days for 6 cycles

Experimental: TC
Paclitaxel 175 mg/m^2 3h d1
Carboplatin AUC 5 d1

Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer

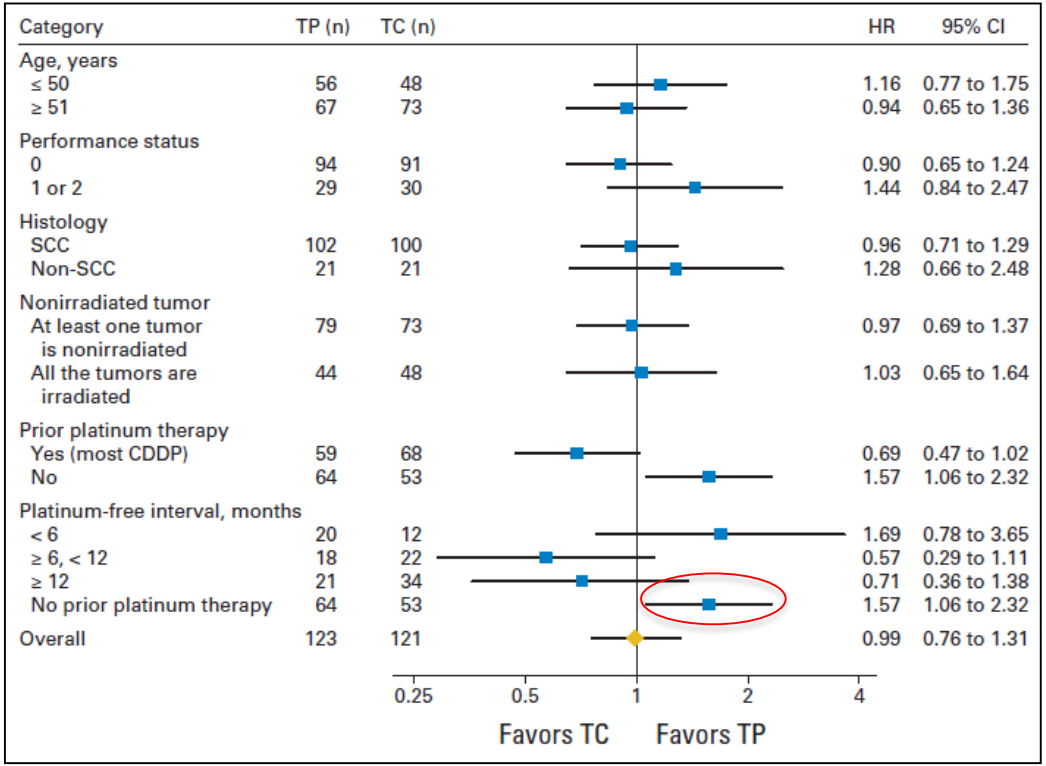
Overall survival



Kitagawa et al, JCO, 2015.

Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer

Subgroups analysis of overall survival



Kitagawa et al, JCO, 2015.

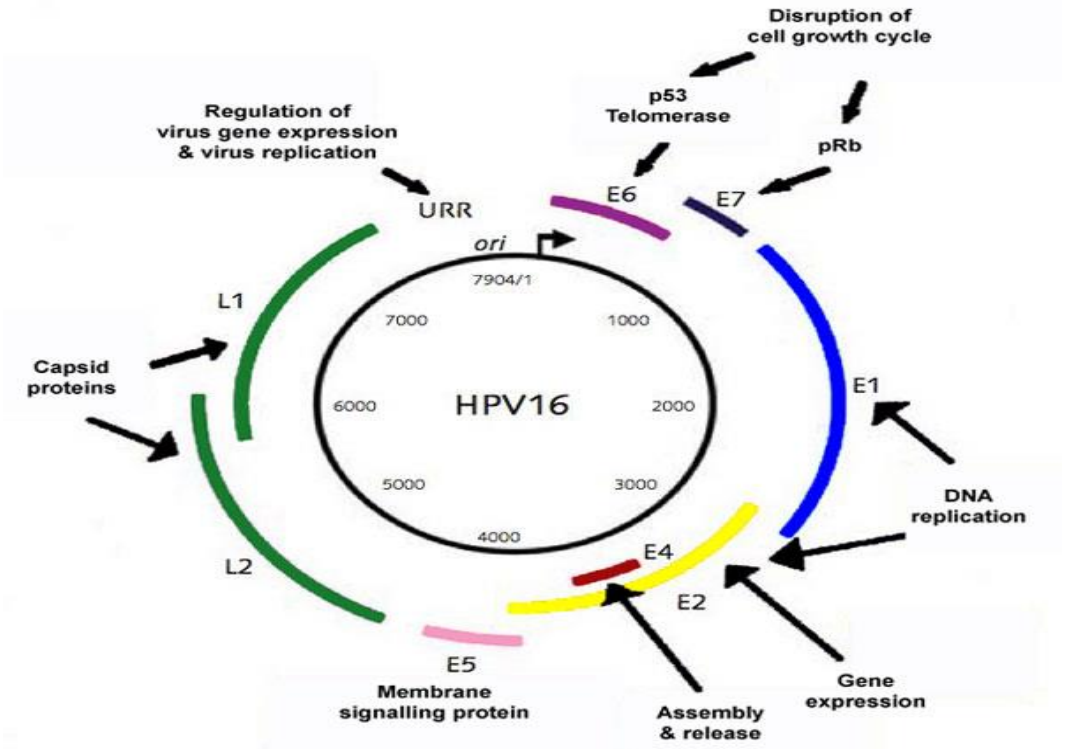
Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer (JCOG 0505)

Conclusions

- The trial demonstrated a statistically significant non inferiority of overall survival of carboplatin / paclitaxel compared to standard cisplatin / paclitaxel
- Carboplatin / paclitaxel did not require patient hydration and hospitalization
- Carboplatin / paclitaxel can be a standard treatment option but only in patients pretreated with a cisplatin-based treatment.

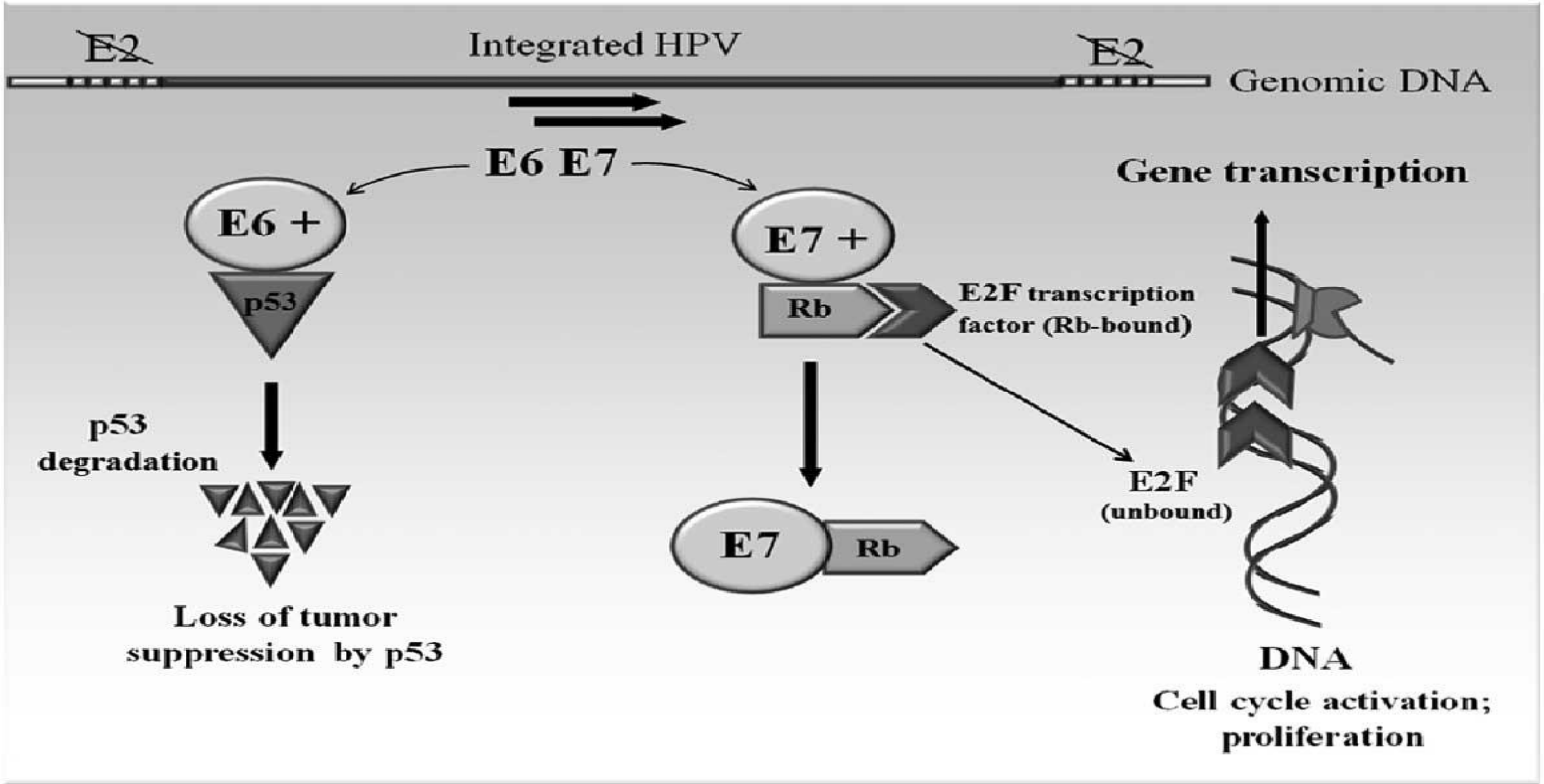
Kitagawa et al, JCO, 2015.

Signaling pathways of high risk HPV oncogenes



High risk HPVs encodes two known viral oncogenes, E6 and E7. E6 protein inactivates p53 mediated DNA damage and apoptosis pathway, while E7 protein inactivates pRb mediated cell cycle regulation pathway

HPV-induced oncogenesis: cellular events



Why T-cell based immunotherapy is promising in cervical cancer?

The HPV oncoproteins E6 and E7 are attractive therapeutic targets because:

- Completely foreign viral protein
- No antigen loss

Still limited results with vaccines because of low vaccine induced immune-response and tumor mediated immuno-suppression

Immunotherapy for cervical cancer

Several T cell based immunotherapy approaches in early clinical trials

- Checkpoint inhibitors / immune modulators
- Therapeutic vaccines
  - Bacterial vector
  - Viral vector
  - Peptide / protein based
- Adoptive T cell therapy

THANK YOU

ESGO 20

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NOVEMBER 04-07, 2017 | VIENNA, AUSTRIA

European Gynaecological Oncology Congress 2017

VIENNA, AUSTRIA

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FIGO Cervical Cancer Staging

Stage I

The carcinoma is strictly confined to the cervix
(extension to the corpus would be disregarded)

Stage IA: Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm

- **Stage IA1:** Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
- **Stage IA2:** Measured stromal invasion of >3.0 mm and ≤5.0 mm with an extension of not >7.0 mm

Stage IB: Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*

- **Stage IB1:** Clinically visible lesion ≤4.0 cm in greatest dimension
- **Stage IB2:** Clinically visible lesion >4.0 cm in greatest dimension

Stage II

Cevical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina

Stage IIA: Without parametrial invasion

- **Stage IIA1:** Clinically visible lesion ≤4.0 cm in greatest dimension
- **Stage IIA2:** Clinically visible lesion >4 cm in greatest dimension

Stage IIB: With obvious parametrial invasion

Stage III

The tumor extends to the pelvic wall and/or involves lower third of the vagina and or causes hydronephrosis or non-functioning kidney**

- **Stage IIIA:** Tumor involves lower third of the vagina, with no extension to the pelvic wall
- **Stage IIIB:** Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

Stage 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

- **Stage IVA:** Spread of the growth to adjacent organs.
- **Stage IVB:** Spread to distant organs.

Titolo?

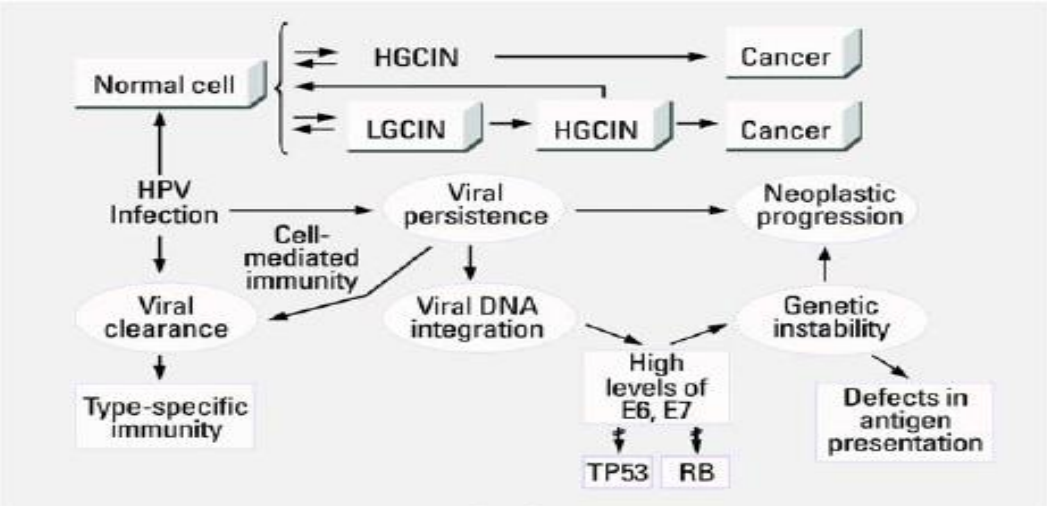

Fig. 5.04 Mechanisms of human papillomavirus (HPV) carcinogenesis. LG = Low grade, HG = High grade, CIN = Cervical intraepithelial neoplasia, RB = Retinoblastoma gene.

Titolo?

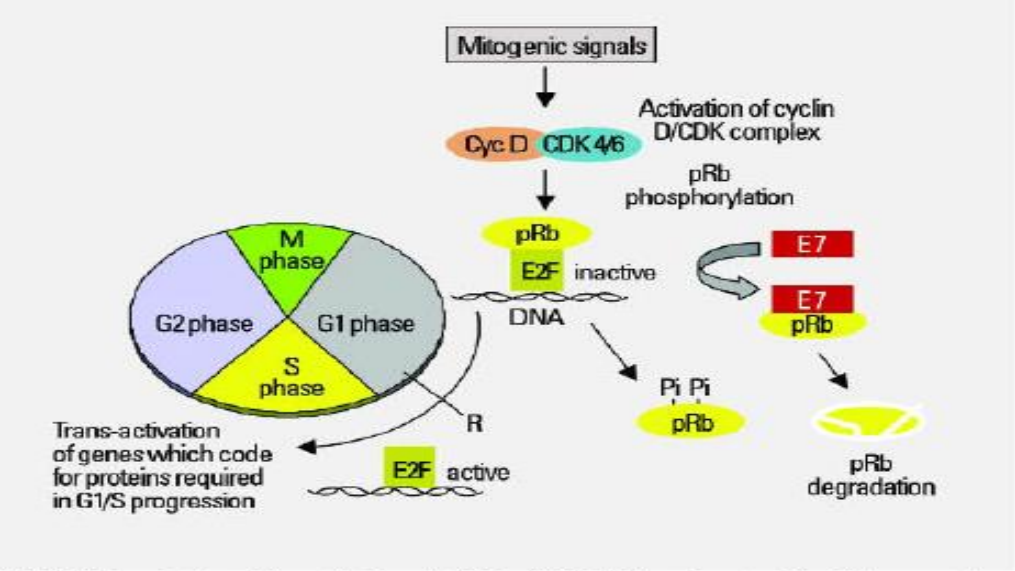

Fig. 5.03 Deregulation of the restriction point (R) by HPV16 *E7*. In quiescent cells, pRb is present in a hypophosphorylated form and is associated with transcription factors, e.g. members of the E2F family, inhibiting their transcriptional activity. When quiescent cells are exposed to mitogenic signals, G1 specific cyclin D/CDK complexes are activated and phosphorylate pRb in mid-G1 phase, causing release of active E2F and progression through the restriction point (R). E7 binding to pRb mimics its phosphorylation. Thus, E7 expressing cells can enter S phase in the absence of a mitogenic signal. From M. Tommasino {2938a}.