

Management of Cancer of the Uterine Cervix

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Optimal management of cervical cancer

- Precisely evaluating tumour extent
- Carrying out tailored treatment
- Deliberate post-therapy surveillance
- Accurate restaging
- Appropriate salvage therapy



Stage	Patients (n)	Mean age (yrs)	5-y OS (%)	HR ^a (95%CI)
Ia2	275	45.4	94.8	0.4 (0.3-0.7)
Ib1	3020	48.6	89.1	} Reference
Ib2	1090	46.8	75.7	
IIa	1007	54.4	73.4	1.9 (1.6-2.2)
IIb	2510	53.5	65.8	2.7 (2.4-3.0)
IIIa	211	60.3	39.7	5.3 (4.3-6.5)
IIIb	2028	56.6	41.5	5.3 (4.7-5.9)
IVa	326	59.5	22.0	11.7 (9.9-13.8)
IVb	343	56.8	9.3	20.3 (17.4-23.7)

2006 FIGO Annual Report. Carcinoma of the cervix uteri: Patients treated in 1999-2001. Survival by FIGO stage, $n = 11639$.

^a Hazards ratio and 95% CI obtained from a Cox model adjusted for age and country



FIGO staging system

- The FIGO clinical staging system of cervical cancer is created for **classification and comparing results** among different hospitals and modes of therapy
- Early-stage cervical cancer can be equally cured by either radical surgery or RT. Careful selection (by pretreatment parameters) is necessary to **avoid using both surgery and RT on these good-prognostic patients**



Prognostic factors in cervical cancer

- Stage
- Histologic type (small cell, AD/ASC)
- parametrial extension
- Pelvic lymph node metastasis
- Para-aortic lymph node metastasis
- Grade of differentiation
- Depth of cervical stromal invasion
- Lymphovascular permeation



Cervical Carcinoma: Routine Pretreatment Evaluation

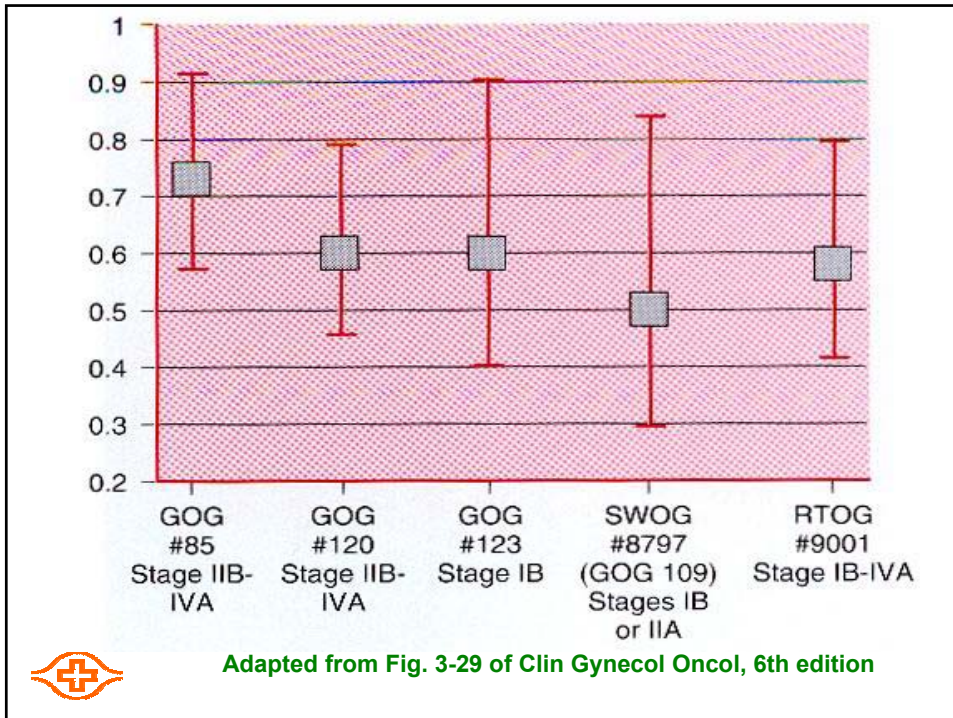
All cases	Stage IIb-IV and bulky Stage IIa, Ib2 (optional)
Physical & Pelvic examination	Cystoscopy proctoscopy
Routine laboratory tests	(CT scan or MRI) (Bone scan)
Chest X-ray	(PET)
IVP	
SCC, CEA, CA125	



Basic Principles of Managing Advanced Cervical Carcinoma

- 1) Exclude the presence of distant metastases
- 2) Define the extent of regional lymph node involvement
 - Paraortic LNs
 - Common iliac LNs
 - Bulky pelvic LNs
- 3) Primary tumor control except small IIb, all others 30~40% initial failure
 - Radiosensitizer, Neutron, hyperthermia, concomitant chemotherapy
- 4) Prophylaxis of occult systemic disease





Interval evaluation of cervical cancer following RT

Year	Frequency	Examination
1 (0-6m)	1-2m	PE+PV exam, Pap colposcopy, Bx, tumor markers, sonography
	(7-12m)	3m
		CBC, SMA-12, CT Scan at 1Y (MRI)
2	3m	PE+PV exam, Pap, Tumor markers (special exams when indicated)
3	4m	PE+PV exam, Pap, tumor markers
4-5	6m	PE+PV exam, Pap
>5	yearly	PE+PV exam, Pap

- **Use of CT/MRI, FDG-PET or routine surgical staging has not been proven by randomised trials to be beneficial to overall survival**
- **Early detection of recurrence or more accurate initial staging or re-staging on relapse does not guarantee improved long-term outcome**



Computed Tomography

- **Abdominal and pelvic CT scan is valuable in the assessment of retroperitoneal lymph nodes, liver, spleen**
- **Poor in evaluating tumor size and depth of stromal invasion at cervix**

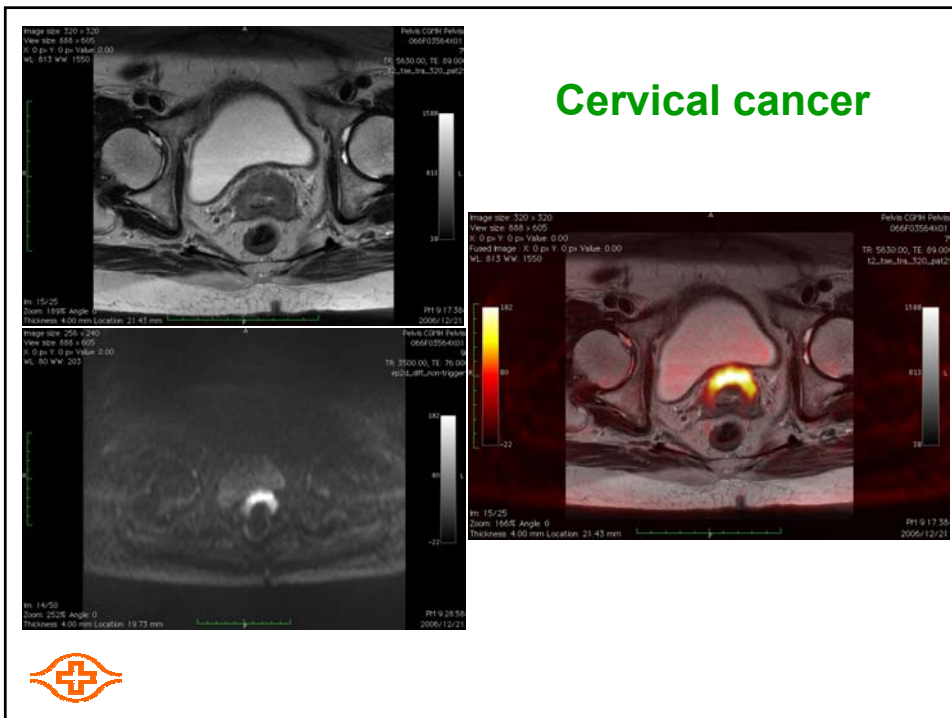


MRI with diffusion weighted imaging (DWI)

- Depth of stromal invasion: Neither CT or MRI accurate; Spearman correlation of multi-observer diameter measurement: MRI 0.58 vs CT 0.27 (*ACRIN 6651/GOG 183 Intergroup Study-Mitchell, et al. JCO 2006*)
- Restricted proton movement in membrane, organelle, cytoskeleton and macromolecules
- Increased intra- to extracellular volume ratio
- Restriction: decreased apparent diffusion coefficient (ADC) value



Cervical cancer



Nanoparticle-enhanced MRI

- 29 cervical cancer and 15 endometrial cancer
- MRI was performed before (size criteria) and after USPIO before lymphadenectomy
- **25%** patients with **LN metastasis**
- A node-by-node basis
 - Sensitivity was **93% for USPIO** and **29% for size criteria alone**
- Role of USPIO for early-stage non-bulky cervical cancer
 - Unknown

Rockall et al. JCO 2005; 23:2813-21



Positron emission tomography

Tracer	Biologic analogue	Effect
¹⁸F-FDG	Glucose	Glycolysis, tumor or inflammation
¹⁸ F-fluorouracil	Uracil	Binding to thymidylate synthetase, predicting tumor response to 5-FU
¹⁸ F-annexin V	Annexin V	Apoptotic cell death
¹⁸ F-misonidazole	NA	Tissue hypoxia
¹⁸ F-choline	Choline	Cell membrane metabolism, tumor proliferation
¹¹ C-acetate	Acetate	Lipid synthesis, tumor proliferation

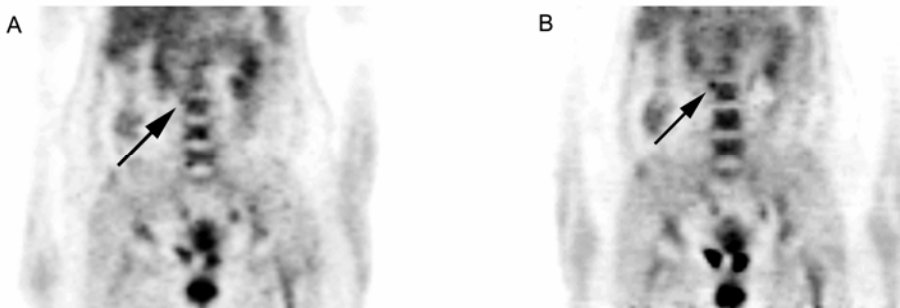


Method of PET Scanning at CGMH

- Catheterization and diuretics
- Fasting 6 hours
- Intravenous administration of 370 MBq of FDG
- PET was performed at 40-min after injection (PET-CT was performed at 60-min after injection)
- Delayed PET (or PET-CT) was added if necessary
- For dual-phase PET, early and late images were combined for interpretation

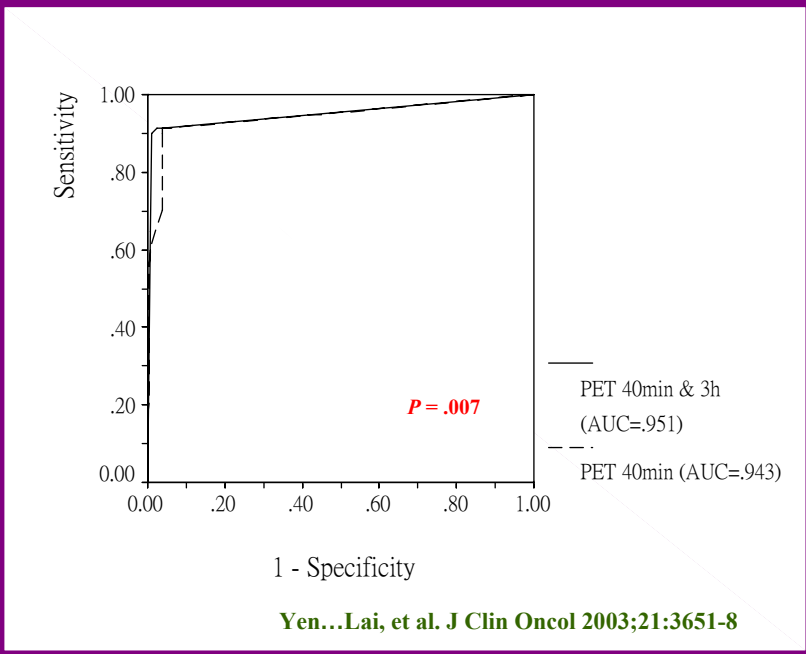
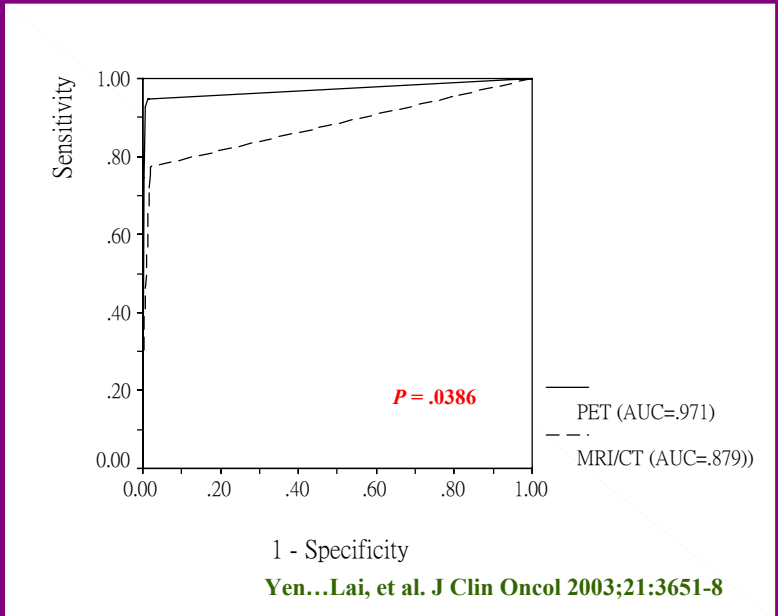


Dual-Phase PET Scan versus Conventional PET



Yen et al. J Clin Oncol 2003;21:3651-8





POTENTIAL TIME POINTS OF UTILIZING PET IN CERVICAL CANCER

- a) For FIGO stage IB-IIA (> 4cm) and stage IIB-IV
PET can be added to conventional CT/MRI for primary staging or monitoring response to NAC
- b) For FIGO stage IB-IIA (<= 4cm)
limitation of PET to detect micrometastasis will reduce the benefit (Chou,...Lai, et al. JCO 2006)
- c) Routine follow-up of high-risk group with PET after definitive treatment
low PPV 35% (Ryu et al. J Nucl Med 2003)
- d) Extrapelvic spread at presentation yet limited to an isolated site
such as paraaortic, supraclavicular or inguinal lymph nodes



POTENTIAL TIME POINTS OF UTILIZING PET IN CERVICAL CANCER

- e) When clinical suspected recurrence
e.g. SCCAg elevation (Chang,...Lai et al. Cancer 2004)
- f) Restaging after documented relapse
55% modified treatment due to PET (Lai et al. Cancer 2004)
- g) Follow-up after salvage therapy
to consolidate retreated site or detecting treatable new lesions (Lin,...Lai, et al. IJGC 2006)



Conventional Role of Chemotherapy in Cervical Cancer – Palliation for Advanced and Recurrent Carcinoma

- **Cisplatin** is the most active single agent
- Duration of response 3-6 months
- Survival 5-9 months
- Combination regimen has been shown to be superior to single agent cisplatin (cisplatin+**topotecan** vs cisplatin improved response rate [27% vs 13%], PFS [4.6m vs 6.9m] and OS [9.4m vs 6.5m]– JCO 2005)



Neoadjuvant chemotherapy (NAC) in early-stage bulky tumor or locally advanced cervical cancer: a systemic review and meta-analysis

- 5 phase III trials (NAC+surgery)
- Cisplatin-based NAC was beneficial if the dose intensity of cisplatin level kept above **25 mg/m²/week**
- Combined HR=0.65, 95% CI 0.53-0.80, P = 0.0004
- **Dose intense and short cycle**

Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration. Eur J Cancer 2003;39:2470-86.



Neoadjuvant Chemotherapy of Previously Untreated Cervical Cancer: *randomized controlled studies*

Author	Year	Patient selection/ number	Regimen/ cycle	Rate of post-op RT of NAC arm	Results
Sardi	1993	IB tumor >3 cm by ultrasound / NAC+RS+RT (76) RH-PLND+RT (75)	POB/q10d X3	NAC: 100%	4-y OS NAC: 88% Control: 70% p=0.44 Tumor >4x4x4 cm: NAC: 88% Control: 60% P = 0.05
Chang (CGMH)	2000	IB-IIA >= 4 cm/ NAC+RH-PLND (68) RT alone (62)	POB/q10d X3	NAC: 28% adjuvant RT	2-Y OS NAC 81% RT: 84%, p = 0.76 Projected 5-Y OS: NAC 70% RT: 61%, p = 0.77
Benedetti- Panici	2002	IB2-III/ NAC+RH-PLND (210) RT alone (199)	Cisplatin-based (P>=240mg/m2)/ in 6-8w	NAC: 18% adjuvant RT	5-Y OS NAC 58.9% RT: 44.5%, P= 0.007 5-Y PFS NAC 55.4% RT: 41.3% P = 0.02



Experiences of Using NAC in CGMH

- All stage IB or IIA bulky (>=4 cm) cervical cancer treated with POB q10D (1988-1999) at CGMH
- 162 Pts received NAC, 5 ineligible, 151 explored, 146 received RH-PLND
- Overall response rate: 79.4%
- 5-Y OS: 69%; 5-Y RFS 65%
- Poor prognostic factors by multivariate analysis: Pre-NAC, age <35 Y, tumor size > cm, and AD/ASC, Post-NAC, LN metastasis and parametrial extension
- 5-Y OS **age <35 or AD/ASC vs age >=35 and SCC: 39% vs 79% (p = 0.0003); RFS: 40% vs 72% (p = 0.001)**
- Future trials comparing NAC+RS with CCRT should be narrowed down to age >=35 and SCC and stratified with tumor size (> 5 cm, < 5 cm)



Huang HJ, ... Lai CH. *IJC* 2003;13:204-11.

Poor outcome in stage III-IV cervical carcinoma treated with NAC

- The prognosis of those who received NAC with an end to perform RH-PLND but were eventually treated with RT for poor response were extremely poor
- Even tumor can be shrunken down for resection, but **postoperative RT is still indispensable**, which results in **3 treatment modalities** (NAC+S+RT) achieved what can be obtained with **2 modalities** (CCRT)
- 5-Y OS: **IIIB 20%** (Etcheheverry, et al. *IJGC* 2000)
- 5-YOS: **IIIB 36%** (Benedetti-Panici, et al. *Gynecol Oncol* 1996)
- 2-Y OS: **III 43%, IV 0%** (Bloss, et al. *Gynecol Oncol* 1995)



Stage	Patients (n)	Mean age (yrs)	5-y OS (%)	HR ^a (95%CI)
Ia2	4	40.5	100.0	
Ib1	76	52.0	68.1	} Reference
Ib2	165	45.7	69.9	
IIa	153	54.0	70.6	0.9 (0.6-1.4)
IIb	570	52.2	70.5	0.8 (0.6-1.1)
IIIa	63	55.8	48.2	1.6 (1.0-2.5)
IIIb	472	53.1	50.2	1.7 (1.2-2.3)
IVa	67	54.5	36.2	2.6 (1.7-3.9)
IVb	85	54.0	14.6	4.8 (3.3-6.9)

2006 FIGO Annual Report. Carcinoma of the cervix uteri: Patients treated in 1999-2001. Survival by FIGO stage (**chemo-radiotherapy**), *n* = 1655.

^a Hazards ratio and 95% CI obtained from a Cox model adjusted for age and country



Salvage Therapy

- Management of recurrences depends on the extent of disease, primary treatment, and performance status/comorbidity
- CCRT achieves significantly better outcome than radiation alone in patients with recurrences after primary radical hysterectomy (*Wang, ...Lai, et al. Am J Obstet Gynecol 1999*)
- Isolated PALN metastasis and local recurrence confined to cervix were associated with better outcome in failure after definitive RT (*Hong, ...Lai, et al. Int J Radiat Oncol Biol Phys 2005*)



Salvage Therapy

- Pelvic exenteration is usually necessary for pelvic recurrence after definitive RT or surgery plus adjuvant RT
- RAH s/p radiotherapy failure can be applied to very limited selected cases: 57% survival but 47.6% fistula
 - 1) Ib, IIa initial stage
 - 2) Recurrent tumor no greater than 2 cm
 - 3) Willing to take risk of high fistula rate and possibly compromised cure rate



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