CANCER of CERVIX

CANCER of CERVIX- CARCINOGENESIS

C Woodman et al (Lancet 2001;357:1831-6) Natural history. N=1075 sexually active females, median age 18 yo, initially HPV negative. Conversion rate at 3 y 44%. High grade CIN 28/246; RR for HPV 16 8.3 at 6-12 mo after infection

A Hildeshein et al NCI Bethesda (JNCI 2001;93:315). European variant of HPV (substitution G to A at 7521) had a cancer risk of HR=1. Non European variant (different or multiple substitutions) had a cancer risk HR=11.

P Sasieni & J Adams (ICRF) (Lancet 2001;357:1490-3). Adenocarcinoma increased x 14 in women 25-54 yo. It was non existent in older women, and biologically different than squamous cell carcinoma. NO reason fund for adenocarcinoma increase in incidence.

M Nobbenhuis et al (Lancet 2001;358:1782-3). HPV clearance precedes 6 mo the cytological regression and disappearance of mild to moderate dyskaryotic cervical smears. Recommend HPV testing at 6 mo of diagnosis.

Cuzick J et al (Ann Oncol 2001;12:1511-4). HPV testing: Triage of borderline or low grade lesions (sensitivity 65-95%); primary screening test (sensitivity 80-100%, specificity 82-95%; that is a 10% higher sensitivity and a 10% lower specificity than cytology); follow-up CIN (negativity after therapy is an equivalent of cure).


D Solomon et al ALTS Group (JNCI 2001;93:293-9). HPV test obtained by hybrid capture 2TM and thin layer cytology: Sensitivity 96.3% referring to colposcopy 56.1% with CIN3. Cytology repeat had a sensitivity of 44% referring to colposcopy 6.9%.

V Moreno et al IARC Lyon (Lancet 2002;359:1085-192). HPV infection of high risk population: Oral contraceptive use <5y not increasing risk for insitu/invasive cervix cancer. IN 5-9 y user OR=2.82 and >10 y use OR=4.03.


M Sherman (JNCI 2002;94:102-7). HPV testing at 1.0 pg/mL threshold would decrease ASCUS referral to 31% in 30 yo and 65% in younger women. Important to narrow the CIN3 detection range.

M Sherman et al (JNCI 2003;95:46-52). HPV & PAP can select for a q 6 mo testing in CIN3 or cancer . When both are normal testing can be delayed for 2-3 years.


N Munoz et al (NEJM 2003;348:518-27). HPV risk of cervical cancer: (>90% of cases are positive) Types HPV 16 (54%), 18 (11%), 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82 and probably 26, 53 & 66, and combinations. HPV low risk: 6,11, 40, 42, 43, 44, 54, 61, 72, 81, CP 6108, 70 & 73. Important for screening.
HJ Au et al (Cancer 2003;97:1672-80). DNA chip microarray to diagnose HPV type identified 22 HPV genotypes (sensitivity 96%, negative predictive value 97%).

J Cuzick et al HART Study (Lancet 2003;362:1871-6). N=11085, >30 yo. High risk HPV+ and borderline cytology, randomized to Colposcopy or surveillance/repeat at 12 mo. Noe progressed and 40% became HPV negative. HPV testing>cytology in sensitivity (97 vs 76%) and HPV testing<cytology in specificity (93 vs 95% for CIN2).

M Arbyn et al (JNCI 2004;96:280-93). ASCUS vs CIN2+. Comparison of hybrid capture II assay (virology) (sensitivity 94%, specificity 67.3%) vs repeat PAP smear (sensitivity 81.8% and specificity 57.6%).

S Vinokurova et al (JNCI 2005;97:1816-21). N=1500 anogenital lesions, 7 had high grade prior cervix diagnosis. HPV 16-18 integration studies identified HPV DNA identical integration loci in vagina and cervix indicating same clonal origin. Dysplastic lower genital lesions might be spreading from cervix.

SJ Goldie et al (NEJM 2005;353:2158-678). Cost effectiveness of cervical cancer screening: Single time at 35 yo reduced cancer 25-36% at 550$ cost each year of life saved. Two screens at 35-40 yo reduced additional 40% at a very cost effective rate. Three screens reduced 50%.


G Ronco et al (JNCI 2008;100:492-501). N=24,661, women 35-60 yo. Randomized: Cytology + or ASCUS ➔ referred to colposcopy vs HPV high risk DNA (Hybrid capture) > 1pg/mL ➔ referred to colposcopy. HPV detection sensitivity 1.92, positive predictive value 0.80 for 1 pg/mL & sensitivity 1.81, positive predictive value 0.99 for 2 pg/mL. RR=3.5 for 1 pg/mL in 25-34 yo, and frequent regression of CIN2+ indicated need for delayed colposcopy.

**CANCER of CERVIX- VACCINE**

L Koutsky et al USA Group (NEJM 2002;347:1645-50). N=2392, 16-23 yo, M F up 17.4 mo. Randomized to placebo 3 doses (HPV infection 3.8%, 9 cases CIN) vs vaccination HPV 16 virus like particle (capside without DNA) 40 ug/dose x 3 at 0, 2 and 6 mo ((HPV infection 0%). Great expectations with vaccines for HPV 16, 18, 31, 33 & 45, with a reduction of cancer >85% at 10 y. HPV 6 & 11 vaccine can protect genital warts.


JT Schiller & DR Lowly (Ca Res 2006;66:10229-32). Vaccines use virus like particles based on L1 protein of HPV16 & HPV18, representing 70% of all cervix cancers. Indication based in: duration of protection unknown (only 1.5 y in follow up trial for Gardasil); Cross protection for other HPV not included (aim is to include other HPV types); mass protection because woman mucosal excretion is based on a 10% Antibody transudation; do not induce regression of established lesions (only prophylactic use); unknown the effect on PAP screening; difficult Third World Coverage...
GARDASIL (Merck) (use alum adjuvant) approved June 2006. HPV 16,18, 6 & 11 for cervical-vulvar-vaginal dysplasia and genital warts in women <26 yo. Vaccine protection 99%. Phase III in N=25000/33 countries, randomized trials FUTURE vs placebo (cancer 0/1200 vs 21/1200 at a 17 mo F-up). Cost $360 for 3 vaccine series.

CERVARIX (Glaxo Smith Kline) use AS04 a proprietary adjuvant, approved 2007. HPV 16 & HPV 18. Phase III in N=30000/14 countries, randomized trials vs placebo (HPV-008) indicated vaccine 0/481 cancer vs 13/470 in placebo at a M F up 4 y).

FUTURE STUDY I (NEJM 2007;356:1928-43). R placebo controlled: N=5455, women 16-24 yo. End pont: genital warts, CIN vaginal/vulvar/adenoc/ cancer with HPV 16, 18 and infection with HPV 6 & 11. Vaccine (no lesions end point 100%; intention to treat any HPV lesion decreased 34% and efficacy decreased incidence 20%) vs placebo.

FUTURE II STUDY GROUP (NEJM 2007;356:1915-27). Quadrivalent vaccine HPV 16, 18, 6 & 11. Randomized double blind, 3 doses, N=12.167, women 16-26 yo, F up average 3 y. Vaccinew given d1, mo 2 & mo6. End point was CIN 2-3, adenoi in situ, cervix cancer HPV 16-18. Vaccine end point 98%, intention to treat decreased incidence 44% and efficacy decreased 17%. Proposal was to improve upon the results by selection of unexposed women, allowing a 100% protection.

JJ Kim & SJ Goldie (NEJM 2008;359:821-32). HPV vaccination in preadolescent girls (12 yo) is cost effective with catch-up efforts at 18-21 yo. Assumptions: Vaccine protects all life, not waning with time; no other strains of HPV 16 & 18 will arise; no alterations of the natural immunity towards HPV reactivity; continuing screening practices; vaccine can prevent cancer and death ultimately (now yet unproven). Cost gain estimations are: At 12 yo 43.600$/QALY; at 18 yo 97.300$/QALY; at 21 yo 120.400$/QALY; at 26 yo 152.700$/QALY; at 12 yo 43.600$/QALY. Need years of follow up studies to get an answer.

CANCER of CERVIX-EARLY STAGE

J Green et al (Lancet 2001;358:781-6). Meta-analysis of concomitant ChX + RT. ChX+RT improved OS (OR 0.71) with/without CDDP, and better results in only Stage I series. Absolute benefit in PFS 16% and in OS 12%, with a reduction in local/distant failures.

C Levenback et al (JCO 2002;20:688-93). N=39. Sentinel ly no in patients undergoing radical hysterectomy + lymphadenectomy. SLN was identified in 85%: 55% had bilateral in either iliac, obturator or parametrial sites (80%) and the rest was in the common iliac & paraortic sites. In 8 patients (21%) had metastasis and in 5 only the SLN was positive. Sensitivity 87.5%, negative predictive value 97%.

D Grisaru et al (Cancer 2003;97:1904-8). Stages IA2-IB1 & IB2. Pathologicval score: Tumor grade >2, capillary lymphatic invasion (HR 2.4), Ly no + (HR 2.) Depth of invasion > 10 mm (HR 1). 5yOS score0= 98% (5yDFS 98%); score1= 96% and 86%; score2= 86% & 82%; score 3= 84% & 64%; and score4= 66% & 50%. Importance for selecting adjuvant therapy.

A Rockale et al (JCO 2005;23:2813-21). USPIO (Ultrasmall particles of iron oxide, FERUMOXTRAN 10, in MRI enhanced detection of endometrial/ cervix cancer lymph node mets: Sensitivity 90-100%, specificity 85-94%, positive predictive value 71-82%, negative predictive value 95-100%.

CH Lai et al (JCO 2007;25:3628-34). N=1067, Operable Stage I-IIA cervix cancer, M F up 77 mo. HPV DNA+ 95.1% (9.6% multiple serotypes), HPV 16= 63.8%, HPV 18=16.5% had worst prognosis. Scoring system: Age<45 (OS HR=1.7, RFS HR=), FIGO I vs II (OS HR=1.8, RFS HR=2.6), Depth <1.3 mm (OS HR=2.4, RFS HR=2), Parametrium + (OS HR=2.6, RFS HR=)},
HPV-18 (OS HR=1.7, RFS HR=1.8), Tumor < 2cm (OS HR=/, RFS HR=2.6), Grade 1 (OS HR=/, RFS HR=2.1). Results: Score 0-2 (5yOS 97.5%, 5yRFS 95.9%), score 3 (5yOS 87.6%, 5yRFS 86.7%), Score 4-7 (5yOS 77.9%, 5yRFS 72.7%). Require neoadjuvant/adjuvant therapy scores >2.

**CANCER of CERVIX – LOCALLY ADVANCED**

A Westermann et al (Cancer 2005;104:763-70). N=68. Cervix cancer stages IIB-IVA. EBRT + Brachy >86.7 Gy + CDDP 40 mg/m2 + others x 4 simultaneous + Weekly hyperthermia x 4. Results: CR 90With a MF up 538 d, 74% ANED & 84% OS. Randomized study to confirm tyhere is a 15% improvement in OS.

A Buda et al (JCO 2005;23:4137-45). N=219, M F up 43.5 mo. Randomized to IFX 5 g/24 h + CDDP 75 mg/m2 (CR 23%) vs CDDP 75 mg/m2 + IFX 5 g/24 h + TXL 175 mg/m2 (CR 48%, failure rate HR=0.75, Death rate HR=0.66).

A Nogueira et al (Clin Ca Res 2008;14:6324-9). N=15., Stage IIB-IIB. Erlotinib 50-150 mg qd + CDDP 40 mg/m2 wkly x 5 + RT 45 Gy (in 25 F) + Brachy 4 F x 600 cGy. Well tolerated, rash grade 2 in 50%, grade 3 in 14%; diarrhea 86%. CR 91.7% + PR 8.3%. At 1 y 2/12 PD.

**CANCER of CERVIX – CHEMOTHERAPY**

HJ Long III et al (JCO 2006;23:4626-33). Randomized study using CDDP 50 mg/m2 q 3 wk (N=146, MOS 6.5 mo, MPFS 2.9 mo, OR 13%), vs CDDP 50 mg/m2 + TPTC 0.75 mg/m2 d 1-3 q 3 wk (N=147, MOS 9.4 mo, MPFS 4.6 mo, OR 27%), and vs MTX + VBL + DOPX + CDDP (MVAC) q 4 wk (closed early due to 4/63 deaths).

H Long III et al (JCO 2007;25:2966-74). Review chemotherapy: Single agent mostly CDDP failures OR 8-15%, MST 5.5-7 mo; Doublets CDDP + another agent (TXL, TXT, IFX, GEM, CPT, 5FU, MitoC) OR 30-45% MST 7-10 mo; Triplets CDDP + others OR 55-65%, MSTY 11-12 mo. Not better for quartlets. Randomized stutdies: CDDP+IFX+/-Bleo OS 8.5 mo, no differences; CDDP+/-TXL improvement OR 36% vs 19%, OS 9.7 vs 8.8 mo; CDDP +/TPTC also improvement OR 27% vs 13% nad OS 9.4 vs 6.5 mo.

**CANCER of CERVIX- IMMUNETHERAPY**

MJP Welters et al (Clin Ca Res 2008;14:178-87). HPV16 E6 and E7 long peptide vaccine + Montanide ISA-51 adjuvant. Evaluated by Elispot IFNgamma, Tcell populations including CD4, CD8, CD25 and Foxp3). T cell responses 6/6 (E6) and 5/6 (E7), lasting >12 mo. Highly immunogenic, but responses were based on T4 subtypes, including T reg phenotype.

G Kenter et al (Clin Ca Res 2008;14:169-77). HPV E6 & E7 sequence peptide 100-300 ug + Montanide ISA 51 adjuvant, q 3 wk x 4 . N=35 end stage cervix cancer. No toxicity. Elispot was positive for all the patients.
CANCER of VULVA

ES Abdel-Hady et al (Ca Res 2001;61:192-6). 5 aminolevulinic acid (PDT) 10/30 OR in vulvar high grade intraepithelial neoplasia (VIN) grades 2-3. NO responses observed in high risk HPV infection and immunosuppression.


Agj Van der Zee et al (JCO 2008;26:884-9). SLNB in early vulvar cancer. N=623 groins/403 patients; T1-2 (<4cm), Lymph node dissection done only when SLNB+. Results: 259 negative SLN: only 6 groin recurrence (2.3%) and 3yOS 97%. Morbidity 11.7% (after lymphadenectomy 34% short term and 0.4% (16.2%) long term. Lymphedema 1.9% (25.2%). Recommended as the standard procedure.

M Van Seters et al (NEJM 2008;358:1465-73). Intraepithelial vulvar neoplasia grade 2-3. Randomized study: Imiquimod 250 mg 5% cream and sulfur 5% in zinc oxide ointment next day (25% reduction in 20 wks 21/26, 81%; histologic regression significant, HPV clearance 58%) vs placebo (no reduction in 20 wks, HPV clearance 8%). Only 3 patients had progression of the lesion to < 1mm (6%). CR was observed in 9 patients (35%) at 20 wks remaining DFS at 12 mo, and PR 46%. Quite active.
CANCER of ENDOMETRIUM

CANCER of ENDOMETRIUM - CARCINOGENESIS

G Mutter et al (JNCI 2000;92:924-31) PTEN mut present in 83% (25/30) endometrial cancer and in 55% (16/29) precancerous lesions. Endometrial cancer lost both alleles in 61%. Early event.

T Minaguchi et al (Clin Ca Res 2001;7:2636-42). N=67. PTEN mut 55%: 57% frameshift, 38% mut 3exon 8 and 17% mut exons 1-3, 19% mut exon 7, 14% exon 5, 8% exon 6. Mut exons 5-7 worst survival.


L Baak et al (Lancet 2005;103:2304-12). Review endometrial intrepithelial neoplasia (1-28% lead to cancer). WHO classification evaluate simple non atypical hyperplasia, complex non atypical hyperplasia, simple atypical hyperplasia and complex atypical hyperplasia. In total 24/477 (5%) developed cancer > 1y after the index biopsy diagnosis According to WHO, 13% with atypia and 2.3% without atypia. A new classification of EIN consider gladular volume, architectural complexity and cytologic (nuclear) abnormality. According to it 19% of EIN developed cancer and only 0.6% without EIN developed cancer, indicating a better discrimination. WHO sensitivity 67%, specificity 76%, positive predictive value 13%, negativa predictive value 98%. EIN sensitivity 92%, specificity 79%, positive predictive value 20%, negative predictive value 99%.

RJ Zaino et al (Cancer 2006;106:804-11). Diagnosis of atypical hyperplasia reviewed by a panel of dedicated pathologists (3 pathologists) had a reproducibility of diagnosis of 40%.

C Trimble et al (Cancer 2006;106:812-9). Review by a panel of pathologists Hysterectomy specimens after Complex Atypical Hyperplasia of Endometrium (CAHE). N=289. Preoperative diagnosis: CAHE 39.8%, less than CAHE 25.6% and adenocarcinoma 29.1%. Hysterectomy: Adenocarcinoma 42.6% and myoinvasive carcinoma 30.9%. Disappointing diagnosis and high incidence of concurrent carcinoma.


C Morison et al (JCO 2006:24:2376-85). Her2 overexpression & amplification present in 43% & 29% papillary serous carcinoma (specially in high grade 31% & 15% versus low grade 3% & 1%) and in 3% & 1% endometrioid carcinoma. OS 5.2 y overexpression nad 3.5 y amplification vs 13 y none. No responses observed with Herceptin in 23 patients with Her2 +/+ tumors.


A Santin et al (Cancer 2007;109:1312-22). Serous papillary ca exhibit Claudin3 and Claudin4 receptors (100% tumors and cell lines). CPE (Clostridium perfringens enterotoxin) is a natural ligand causing tumor cell death. Animal murine model with CPE intratumoral or intraperitoneal
injection caused remissions.

H Hirata et al (Cancer 2008;112:1964-73). CYP1A1 (T/C) decreased OR 0.42 in endometrial cancer respect to controls. CYP1A1 t-A increased risk of endometrial ca. SULT1A1 (14 A/g and 85 C/T) increased risk of endometrial carcinoma. SULT1E1 213 G-A had higher risk also.

CANCER of ENDOMETRIUM: HEREDITARY CANCER


H Hampel et al (Ca Res 2006;66:7810-7). Lynch syndrome in endometrial carcinoma: MSI testing positive (MLH1, MSH2, MSH6, PMS2) tested in 118/543 endometrial cancers and found + in 1, 3 & 6 cases respectively which did not fulfill HNPCC criteria, representing 1.8% of the cases.

K Schmeler et al (NEJM 2006;354:261-9). Lynch syndrome have a 40-60% lifetime risk for endometrial carcinoma and 10-12% lifetime risk for ovarian cancer. N=315 Lynch syndrome patients had hysterectomy and BSO indicating 33% endometrial cancer and 5% ovarian cancer. Effective strategy.

K Lu et al (JCO 2007;25:5158-64). In patients with <50yo with endometrial carcinoma 9% had Lynch syndrome mutations (MSH2, MLH1, MSH6).

CANCER of ENDOMETRIUM – EARLY STAGE

C Creutzberg et al (Lancet 2000;92:924-31). N=714, Stage I grade 1-3, total hysterectomy and BSO without lymphadenectomy. Randomized to EBRT 46 Gy (5y recurrence rate 4%, cancer related deaths 9%, 5yOS 81%) vs control (5y recurrence rate 14%, cancer related deaths 6%, 5yOS 85%). Avoids local recurrence but not OS. Vaginal recurrence 2 yOS 79%.

J Cragun et al Duke University (JCO 2005:23:3668-75). Review series of early stage, no prior RT, no grossly involved lymph nodes at the laparotomy, no systemic metastases, and compared the results of lymphadenectomy >11 lymph nodes vs <11 lymph nodes. Found: no benefit for grades I & II, benefit restricted to grade III & > 11 lymph nodes resected (RR 0.25 for OS). Lymph node metastases: 3% paraaortic and 5% pelvic (indicate the need for a SLNB?). Risk of pelvic recurrence 1% vs 5% according to the extent of lymphadenectomy. Similar vaginal recurrence rates (2 vs 3%). 5yOS 82% for complete lymphadenectomy and 64% for lymph node sampling < 11 lymph nodes. Lymphadenectomy recommended in Stage III patients.

C Creutzberg et al (J CO 2004;22:1234-41). High risk, stage IC, grade 3. RT after surgery. 5y regional relapse 14% (for low grade only 1-3%) and 5y mets disease 31% (low grade 3-8%). Recommend adjuvant RT in high risk patients.

PB Panici et al (JNCI 2008;100:1707-16). N=514, stage I endometrial carcinoma, M F up 49 mo. Randomized study to TAH + BSO (no lymph nodes removed, ly no + 3.2%, 5yPFS 81.7%) vs same+ pelvic lymphadenectomy (median ly no removed 30 (22-44), ly no mets 13.3%, HR 1.2, 5yPFS 81%). No differences in OS is spite of better staging.

CANCER of ENDOMETRIUM – CHEMOTHERAPY
S Wadler et al (JCO 2003; 21:2110-14). TPTC 1.5 mg/m² qd x 5 q 3 wk + GCSF (1.2 when prior RT; MTD 0.8-1 mg/m² x 5 d). N=44 untreated. 7.5% CR + 12.5% PR. OR 20%, MDR 8 mo, MOS 6.5 mo.

G Fleming et al (JCO 2004;22:2159-66). N=237. Randomized study to ADM 60 mg/m² + CDDP 50 mg/m² q 3 wk x 7 (OR 34%, OS 12.3 mo, Febrile Neutropenia 2%, neurologic tox grade 2-3 1-4%) vs ADM 45 mg/m² + CDDP 50 mg/m² + TXL 160 mg/m² + GCSF q 3 wk x 7 (OR 54%, OS 15.3 mo, Febrile Neutropenia 3%, neurologic tox grade 2-3 , 12-27%). Better 3 agents.

M Randall et al (JCO 2006;24:36-44). N=396, operated with <2 cm residual abdominal carcinomatosis, Mfup 74 mo. Randomized to WART 30 Gy + 15 Gy boost (5yDFS 38%, 5yOS 42%) vs DOX 60 mg/m² + CDDP 50 mg/m² q 3 x 7 (%yDFS 50%, HR=0.71; 5yOS 55%, HR=0.68).

HD Homesley et al (JCO 2007;25:526-31). N=179, Stage III-IV, uterine carcinosarcoma. Randomized to TXL 135 mg/m² 3 h iv + IFX 1.6 g/m² x 3 d (OR 88%, MPFS 5.8 mo, MOS 13.5 mo) vs IFX 2 g/m² x 3 d q 3 wk (OR 29%, MPFS 3.6 mo, MOS 8.4 mo, HR death= 0.69, HRprogression= 0.71)