COLORECTAL CANCER

CARCINOMA COLORECTAL- CARCINOGENESIS & MOLECULAR BIOLOGY

R Midgley & D Kerr (Lancet 2000;355:716-9). Poor prognostic factors: mutant K.ras, low TGFa, TGFB positive staining, c-myc amplification, p53 mutation, DCC loss, p27 kip loss, PDGFR+, VEGF+, MMP1, 2 and 9 +, CD44+. Good prognostic factors: Bcl-2, wt p53, E-Cadherin +.

R Gyfe et al (NEJM 2000;342:69-97). CRC mutational pathways: microsatellite instability and chromosomal instability. In N=607 patients <50 yo, microsatllite instability 17%, conferred a better survival (OR=0.42) and had a less advanced stage (fewer ly no mets and distant organ mets).

**B Henderson (Nature Cell Biol 2000;2:653-60), R Roin-Arbesfeld et al (Nature 2000;406;2398-405), W Liu et al (Nature Gen 2000;26:146-7). APC regulates transport of B-catenin (an activator of oncogene transcription at the nucleus) by two active nuclear export sequences. When APC is mutated, B-Catenin accumulates and oncogenes are expressed…

J Askling et al (Lancet 2001;357:262-6). Reviewed N=114.102 relatives of patients with inflammatory bowel disease and found N=560 CRC. Risk for relatives oc Crohn Dx & UC was SIR 0.96 Colon and 0.78 Rectal. Carcinogenesis in IBD involved early p53 mutation.

Salonga D et al (Clin Ca Res 2000;6:1322-7). CRC: TS<4.1x10e-3 had OR 57%; TS low + low thymidine phosphorylase <18x10e-3 had OR 79%, and TS low + Dihydropyrimidinedehydrogenase <2.5x 10e-3 had OR 92%.

R Farrell et al (Lancet 2002;359:331-40). Environmental, microbial and genetic factors in Ulcerative colitis: Recent controlled trials: Adjuvant antibiotics (ciprofloxacin) protects (induces and maintains remission) and are mor effective than placebo in cases resitant to steroids. Probiotics are as effective as mesalazin for maintenance of remission (85% chronic pouchitis compared to 0% placebo). Fish oil: effective in mild to moderate cases in induction or adjuvant use and less effective than sulfasalazine. Heparin, leukotriene inhibitors, platelet activating factors and IL10 are ineffective. Cancer risk in extensive colitis increased x 8y, and left sided x>15 y. Porctitis no special risk. If associated primary slerosing clangitis very high risk. In case of no dysplasia 1-2 y surveillance intervals; otherwise repeat q 6 month and take >20 biopsies, if adenoma is found peform polypectomy and repeat q 2 y. When flat dysplasia, or in case of a mass or adenoma with adjacent dysplasia perform colectomy.

G Traverso et al B Vogelstein (NEJM 2002;346:311-20). APC mutations identified in fecal DNA present in 57% of 28 patients wuth CRC in 18 patients with adenoma, and in none of 28 controls. Early finding.

W Zhon et al B Vogelstein (Lancet 2002;359:219-25). Counting alleles to see imbalances of chromosomes 8p and 18q (technique digital SNP, Exact Science Inc). Group R, stable, N=27, 5 yDFS 100%; L/R loss of one but not both, N=60, 5yDFS 74%; and L, loss of both, N=93, 5yDFS 58%. Very significant differences…

Y Shirota et al (JCO 2001;19:4298-304). Studied ERCC1 and TS mRNA expresión and the response to chemotherapy. ERCC1 (cut-off level 4.9x 10e-3) MST 10.2 mo vs 1.5 mo (above/below),and TS (cut-off level 7.5x10e-3) MST 10.2 mo vs 1.9 mo (above/below).

J Scholmacher et al (JNCI 2002;94:936-42). GSTP1 Ile105 Val polymorphism is associated with better survival in LOHP-5FU treatment.

G Traverso et al B Vogelstein (Lancet 2002;359:403-4). Fecal DNA to detect microsatellite instability in proximal colonic cancer: 17/18 identified correctly.

S Nishizuka et al (Ca Res 2003;63:5243-50). Microarray study indicated villin is useful to distinguish CRC from ovarian cancer in difficult to assign primary tumor cases

Y wang et al (JCO 2004;22:1564-71). Affimetrix UI33a Gene Chip (with 22.000 transcripts) selected Dukes B tumors with poor prognosis with a group of profiling 23 genes (accuracy 78%).

M Garrity et al (JCO 2004;22:1572-82). N=366 patients in randomized adjuvant studies based on 5FU were studied for porgnostic factors. Ki67 (>27 or less), diploid tumors (cytometry), p53, 5FU, Stage 2, Low grade ALL CORRELATED with good survival (OS and DFS). Ki67 and ploidy remained after adjusting for Stage and grade, useful to detect B2 requiring treatment.

RT Chlebowski et al (NEJM 2004;350:991-1004). Short term progestin and estrigen use reduced the risk of invasive CRC cancer.

SC Larsson et al (JNCI 2005;97:1679-87). DM in 15 studies (matched, cohort and case-controls) involving >3.593.000 persons indicated an increased risk of CRC (HR 1.3). No differences found for sex or tumor site.

EK Wei et al (JNCI 2005;97:1688-94). Low adiponectin related to obesity and insulin resistance RR 0.5 CRC risk at highest quintile and lowest quintile.

**F Pages et al (NEJM 2005;353:2654-66). Used high throughput DNA arrays (PCR low density real time mRNA, fluorescense, cytometry, etc to study TIL in CRC. N=959, operable CRC cancer. Vascular emboli, lymph vessel infiltrates, perineural infiltration correlated with survival. In the abscense of them TIL had CD8, IFN regulated factor 1, IFN gamma, granulolysin abd granzyme B but not mediator of inflammation or immunosuppression. The presence of CD45RO+ correlated with no invasion, less pathological stage and better survival. Immuneresponse is frequent in early goor prognostic cases.

G Lanza et al (JCO 2006;24:2359-67). Immunohistochemistry of MSH2 and MLH1 correlated 90% with microsatellite instability. N=718, 393 Stage II and 325 Stage III curative resections. Absence of mismatch repair proteins conferred good prognosis in Stage II CRC with 6 y OS 96% specially in right CR. Adjuvant 5FU improved survival in positive MLH1 and MSH2. Need for using these staining procedures in all CRC reports?.

*AM Jubb et al (JCO 2006;24:217-27). IFL+BV prolonged survival in pivotal trial with N=813. In N=312 tissue samples studied for microvessel density and VEGF expression (tumor as well as stroma) and thrombospondin-2 expression no correlation was found with survival…

J Vignier et al (Clin Ca Res 2005;11:6212-7). ERCC1 codon 118 polymorphism (coding for asparagines): 22% had AAC codon (C/C genotype) and correlated with OLP OR 21.4%; 33% had AAT codon (T/T genotype) and OR 62%; 45% were heterozygous (C/T genotype) and an OR 42.3%.

J Galou et al (Science 2006;313:1960-4). Immune cells at the center and periphery of CRC predict survival. TH1 adaptive immunity CD3, CD8, Granzyme B and CD45RO+ predict OS independently of TNM staging separating a 80-100 OS and a <20% OS groups.

T Watanabe et al (Ca Res 2006;66:9804-8). Microsatellite instability studied by DNA microarray in 84 cancers. Dsitinguished MSI and stable tumors. Proximal and distal MSI tumors had different pattern, even when sharing hMLH alterations.

O Buhard et al (JCO 2006;24:241-51). 5 mononucleotide markers in N=1.206 worldwide populations: no significant alleles found. 60 MSI tumors displayed instability in 4/5 markers. No need of matching normal DNA. Markers were NR27, NR21, NR24, BAT25 and BAT26.

PJ O´Dwyer et al (JCO 2006;24:4534-8). All patients should be tested for UGT1A1*28 allele TA6/TA7 or TA7/TA7 because are slow metabolizers and associate with severe toxicity to CPT11 at therapeutic doses (specially in combination therapy) as compared with the 6/6 allele. It is mandatory…otherwise give less than normal dose (85 mg/m2 wkly, 300-350 mg/m2 q 3 wk or 180 mg/m2 q 2 wk).

N Meropol et al (JCO 2006;24:4069-77). Immunohistochemistry of thymidine phosphorylase expresión (not for thymidilate synthase or dihydropyrimidine dehydrogenase) correlated with OR in CRC (Primary tumors OR =4.7 and mets tumor OR=8.6). Roche Dx, Manheim, Ge)

JA Chan et al (JCO 2006;24:5680-6). HRT use <5 y before the diagnosis of CRC reduced mortality for subsequent CRC (HR=0.64). No effect for longer use, past use or use after the diagnoses.

CARCINOMA COLORECTAL- FAMILIAL CANCER
On-line Mendelian inheritance in man database (OMIM):
www.ncbi.nih.gov/omim
40% of HNPCC clusters have no mutation of MMR nor MSI and are provisionally called HNPCC syndrome type X

G Sienbach et al (NEJM 2000;342:1946-52). Celecoxib in FAP polyps. Randomized study with Celecoxib 400 mg qd x 6 mo (at 6 mo polyp reduction number 28% and size 30%) vs 100 mg qd x 6 mo (polyp number reduction 11.9% and size 14.6%) or placebo x 6 mo (at 6 mo polyp reduction number 4.5% and size 4.9%). APC mutation increase Bcatenin/TCF-4 binding and this complex increase transcription of PPARdelta (peroxisome proliferator activator receptor delta). COX2 inhibitor reduce production of PPARd eicosanoid ligands.

S Lipkin et al (Nature Gen 2000;24:27-35) MLH3 is a DNA mismatch repair gene associated with MSI. Belongs to PMS1 and PMS2 and might explain why these two are associated with low incidence of HNPCC

NM Lindon et al (JCO 2002;20:1043-8). Studied N=1.144 with family cancer risk by immunohistochemistry of MLH1 and MSH2 and MSI. N=350 (30.6% had MSI and 323 (92% sensitivity) in absence of MLH1 and MSH2. N=794 no MSI and specificity was 100%, predictive value 96.7%.

J Sampson et al (Lancet 2003;362:39-41). Registries of UK identified 111/614 families with clinical FAP without APC mutation or vertical dominant transmission and found 25/111 biallelic muitations of MYH gene (base excission repair gene; others are MTH1, OGG1) transmitted by autosomal recessive trait. Require specific testing and counselling and account for a further 5% of inherited CCR.

C Ribic et al (NEJM 2003;309:247-57). MSI found in 95/570 (16.7%) CCR in randomized 5FU adjuvant trials. 42/287 no adjuvant 5FU presented an improved 5yOS 82% vs 58% (HR=0.31), while 53/283 received adjuvant chemotherapy and had a 5y OS 69% vs 69%. 5FU adjuvant do not improve survival in MSI patients

A Umar et al (JNCI 2004;96:261-8). Revised Bethesda guidelines for HNPCRC (Lynch sy) and MSI. Guidelines to test: 1) CRC in pt <50yo; 2) Synchron/metachronous CRC or other (endometrial,stomach, ovary, pancreas, ureter, bile tract, brain, skin adenoma or keratoacanthoma);3) CRC with MSI histology (TUILs, Crohn like reaction, mucinous signet cell differentiation, medulary growth pattern); 4) CRC in >1 1st degree relñative or any other tumor at <50 yo; and 5) CRC >2 relatives with CRC or other tumor at any age

C Gallione et al (Lancet 2004;363:852-9). Juvenile polyposis and hereditary hemorrhagic telangiectasia are bothrelated to MADH4 mutations (SMAD4, BTGF signalling pathway) and have to be stuied together. Juvenile polyposis present with polyps at early life (20-30) and further malignancies, while hereditary hemorrhagic telangiectasia is related to art-ven shunt in lungs, clubbing, cyanosis, and hemmorrhagic complications of lung, GI and brain.

J Plaschke et al (JCO 2004;22:4486-94). MSH6 represent 10% of HNPCC. Median age is 10 y older (54 yo), and have more tumors outside of CRC. Recommend colonoscopy at 1-2 y intervals starting at 20-25 yo, Gyn-US study at 30-35 yo and also study stamach and urinary bladder.

Y Bian et al (JCO 005;23:3074-8). TGFBR1*6ª allele bears increased CRC risk for homozygotes (familial cluster) owing to a proportion of HNPCC. Stuide 208 index case cases and found MMR (MLH1, MSH2, MSH6) in 69%, and TGFBR1*6ª in 6.3%.

H Lynch (NEJM 2005;352:1920-2), H Haryel et al (NEJM 2005;352:1851-60). Recommend routine molecular screenig for all CRC patients. Identified MSI in 208/1066 patinets not fulfilling the Amsterdam criteria, and 23 had germ cell mutations; prband families were tested andf found 57/117 realtives with Lynch syndrome.

J Church (ASCO Teaching Series 2005). Management of polyposis syndromes:
FAP (commercial testing available, yield 95%). Autosom dom. GI adenomas, abdominal desmoids, Gardners, Turcots, Thyroid cancer, adrnal adenomas, CHRPE retinal. Therapy: Treat abdominal desmoids (symptomatic obstruction), prophylactic surgery at 20 yo, ileal pouch or ileorectal anastomosis + antiCOX2, check yearly duodenum (15% large polyps transform in cancer).
MAP (commercial testing) Gne MYH (1P32.1), autosomal recessive. GI adenomas. Therapy: colectomy and ileorectal anastomosis.
Hyperplastic polyposis (MGMT-HPP1), no family history. Hyperplastic polyps and CRC. Therapy: Endoscopic surveillance.
Mixed hereditary polyposis (CRAC1, 15q13-q14) autosomal dom. Adenoma/hamartoma, CRC. Therapy: Colectomy and ileorectal anastomosis.
Peutz Jeghers syndrome (coimmercially avauilable, yield 70%) (STK1 (19p13.3) Autosom dom. Peutz Jeghers hartoma (smooth muscle in polyp), orobuccal pigmentation, ca pancreas, breast, germ cell testis & ovary. Therapy: Endoscopic capsule and surveillance.
Juvenile polyposis: SMAD4, BMPRIA (18q21.1, 10q23) Autosom dom. Juvenile polyps and CVRC.
Cowden disease (PTEN, 10q23.3) autosom dom. Juvenile polyps, lipomas, neurofibromas, GI , thyroid, breast, skin and uterus cancer. Therapy: Check other sites of cancer risk.
Bannayan-Riley-Ruvalcaba syndrome (PTEN 10q23.3). Autosom dom. Juvenile polyps, macrocephaly, lipoma, meningioma and GI cancer. Therapy: Check other sites of cancer risk.
Gorlin syndrome (PTCH. 9q22.1) Autosom dom. Juvenile polyps, nevoid basal cell ca, skeletal abnormalities, cranium and face, GI cancers.

A Storkmorken et al (JCO 2005;23:47705-12). N=250 familial HNPCC. Immunohistochemistry for MLH1, MSH2, MSH6 proteins: Sensitivity 100%, specificity 82%, +predictive valuer 85% (much higher than Amsterdam and Bethesda criteria)

MC Southey et al (JCO 12005;23:6524-32). All patinets <45 yo with CRC were studied with immunohistochemistry for MMR protein expression (MLH1, MSH2, MHL6, and PMS2) and found germline alteration in 18/131, and only 50% fullfilled the Amsterdam

criteria. Therefore recommend routine testing.

JG Park et al (Clin Ca Res 2006;12:3389-93). Small intestine cancer associated to HNPCC is firts diagnosed tumor in 34.1% of cases. Distributrion is different for MSH2 showing increased mutation of codons 626-733, 26.5% vs 2.8%).

H Hampel et al (Ca Res 2006;66:7610-7). MSI and mutation in MMR found in 1.8% of endometrial cancer patients.

CARCINOMA COLORECTAL- PREVENTION

A Schatzkin Et al (NEJM 2000;342:1149-55). N=2079, with prior bx polyp> 6 mo before entering the study. Randomized diet (lowfat & high fiber) Polyp+ 39.7% vs control Ppolyp+ 39.5%. No differences.

P Janne & R Mayer (NEJM 2000;342:1960-8). FAP randomized studies demonstrated decrease in polyps with Sulindac and Celecoxib. Chemoprevention studies not randomized indicated effect for ASA, Folate, Ca, and Estrogens.

C Bonithon-Kopp et al (Lancet 2000;358:1300-6). Randomized N=665 with adenoma bx to 3 y treatment and follow-up colonoscopy. Ca gluconolactate & carbonate (2 g Ca/d) adenoma 176/28 (15.9%), OR 0.66; Fibre (ispaghula husk) 3.5 g/d 29.3% OR 1.67 adverse effect; Placebo 20.2%

J Baron et al (NEJM 2003;348:891-9) Randomized N=1121 with prior adenoma to ASA 81 g/d (New adenoma 38%, RR 59% vs ASA 325 mg/d (new adenoma 45%) and control placebo (new adenoma 47%), RR 83%.

R Sandler et al (NEJM 2003;348:883-90). N=635 prior adenoma. ASA 325 mg/d (adenoma, 17% and > 1cm 6%) vs placebo (adenoma 27%, and > 1cm 12%)

R Chlewoski et al (NEJM2004;350:991-1004). Women Health Initiative Investigation N=16.608, 50-79 yo, intact uterus, randomized to HRT (equine conjugated estrogens 0.625 mg/d + medroxyprogesterone acetate 2.5 mg/d) correlated with 43 CRC (HR=0.56, although tumors were more invasive – C&D 76% and ly no + 3.2) vs placebo with 72 CRC (C&D 48% and ly no + 0.8%)

S Solomon et al (NEJM 2005;352:1071-80). COX-2 inhibition increased risk of cardiovascular death (stroke, MI, heart failure) to 1% placebo, 2.3% clecoxib 200 mg bid, and 3.4% for celecoxib 400 mg bid. Trial of adenoma prevention was interrupted…

D Alberts et al (JNCI 2005;97:846-53). N=1250. Randomized to Ursodeoxycholic acid 8-10 mg/kg/d x 6 mo (adenoma recurrence decreased 12% and dysplasic adenoma incidence decreased 39%) as compared to placebo… Conisder for chemoprevention.

M Bertagnolli et al (NEJM 2006;355:873-84). Prior adenoma removed and stratified for ASA intake, N= 2100. Placebo had adenoma 60.7% and cardiovascular risk 1; celecoxib 200 bid had adenoma 43.2% and CVR 2.6; and celecoxib 400 had adenoma 37.5% and CVR 3.4. Effecttive but with potentially dangerous CVR.

B Psaty & J Potter (Editorial, NEJM 2006;355:950-2). CRC incidence at 3y for no treatment 3.1%, CV events 14.6% and combined 17.7%; for celecoxib numbers were 1.5% CRC, 27,3% CV andcombined 28.8%; for ASA was 1.9% CRC, CV 10.2% and major bleeding 0.3% for a combined 12.4% (advantage).

CARCINOMA COLORECTAL- SCREENING

J Helm et al (Ca Control 2003;10:193-203). CRC screening review: Fecal occult blood 5% positive in 10 y, with 90% false positives (rehydrated 30% positive but no improvement in cancer detection rate). Sigmoidoscopy/colonoscopy detect 94% polyps 1 cm in diameter. Virtual colonoscopy detect 91% polyps 1 cm in diameter with a false positive rate of 10%. Fecal DNA testing in study. Recommendations: Average risk colonoscopy at 50 yo and repeat every 10 y. With one relative >60 yo with CRC begin at age 40 yo; with 2 relatives or <60 yo, colonoscopy q 5 y starting at 40 yo. FAP perform colectomy/ileoanal anastomosis at 35 yo; HNPCRC have CRC 25% at 50 yo and 70% at 70 yo (plus a 30% cance of a second CRC within 10 y nad a 50% chance of CRC within 15 y), uterus cancer 60% at 70 yo and ovarian cancer 12% at 70 yo, so operation has to include colectomy + hysterectomy + ovariectomy.

P Pickhardt et al (NEJM 2003;349:2191-200). N=1233 patients had virtual colonoscopy (sensitivity 93.8% (<1cm) abd 88.7% (6 mm) and also colonoscopy (sensitivity 87.5% (1 cm) and 92.3% (6 mm). Equivalent results…

H Müller et al (Lancet 2004;363:1283-5). Methylation changes in fecal DNA as a screening test had a sensitivity 90% and specificity 77% (25 samples and 25 controls).

T Imperiale et al (NEJM 2004:351:2704-14). Randomized study comparing fecal occult blood (detected 4/31 cancers, 12.9%) and fecal DNA analysis (detected 16/31 cancers, 51.6%, lower than published) and then confirmed it by colonoscopy-biopsy.

N Segnan et al (JNCI 2005;97:347-57). Screening randomized to FOBT (N=2858, +0.43%, CRC 0.35% and adenoma 0.14%) or sigmoidoscopy (N=4466, +0.76%, CRC 0.4% and adneoma 0.51%).

JS Levine et al (NEJM 2006;355:2551-7). Adenomatous polyps guideline surveillance: Small rectal hyperplastic polyps, interval colonoscopy >5y up to 10 y; 1-2 low risk adenoma (tubular, < 1cm), interval 5-10 y; 3-10 low risk adenoma or any high risk (>1cm, tubulovillous, high grade), interval 3 y; >10 adenoma, interval < 3y; and inadequately removed adenomas, interval 2-6 mo.

J Regula et al (NEJM 2006;355:1863-72). Colonoscopy in N=50.148, 40-50 yo with family antecedent of CRC. Advanced neoplasia (defined as CRC, adenoma < 1cm, high grade dysplasia or tubulo-villous adenoma) found in 5.9% of 51-66 yo and 3.4% 40-50 yo; male>female and HR 1.73

CARCINOMA COLORECTAL- PROGNOSTIC FACTORS

T Watanabe et al (NEJM 2001;344:1196-206). P53 and p21cip had no prognostic effect. DCC/BPC4 was present in 155/319 (49%): 39 had no MSI (5 y OS 74%) and 109 had MSI (5 y OS 50%), so that retention of DCC conferred a survival advantage in microsatellite stable CRC (This applies to 39/221 CRC, 17%). In the other hand MSI was identified in 62/298 (21%): TGFB1-RII was mutated in 61% (5 y OS 74%) and no TGFB-RII mutation occurred in 39% (5 y OS 46%), so that mutation of TGFB1-RII conferred survival advantega in MSI CRC treated with 5FU adjuvant chemotherapy (This apllies to 48/298 CRC,16%.

TE LeVoyer et al (JCO 2003;21:2912-9). Reviewed number of ly no from colectomy tissues. Fat clearance techniques show median ly no number obtained is 47. OS increased with the number of ly no studied. IN N1 (1-3 ly no) 8 y OS ranged from 90% (>40 ly no) , 64% (11-40 ly no) and 56% (1-10 ly no). For N2 (>4) 8 y OS ranged from 71% (>35 ly no), to 43% (1-35 ly no). Recommend to study àt least 20 ly no for N0 and 12 ly no for N+

M Ghadimi et al (JCO 2005;23:1826-38). Microarrays (54 genes) used to predict response to 5FU-RT. Prediction of response 83%, sesitivity 78%, specificity 86%, +prerdictive value 78% and –predictive value 86%.

F Rodriguez Moranta et al (JCO 2006;24:386-93). Intensive surveillance after curative resection (CT, colonoscopy) associated with improved survival due to early detection of resectable tumor recurrence (44% in the intensive survey).

CARCINOMA COLORECTAL- SURGERY- RADIOTHERAPY AND ADJUVANT THERAPY

KL Leving et al (Lancet 2004;363:1187-92). Laparoscopic assited colectomy-rectosigmoid (5 y OS 76.1%, 5 y DFS 75.3%) vs open colectomy (5 Y OS 72.9%, 5 y DFS 78.3%). Considered better laparoscopic due to operation time, better/faster recovery, more expensive and equal results in clear distant margin, ly no resection and morbidity…

Clinical Outcomes Surgical Group (NEJM2004;305:2050-9). N=872, 48 hospital, M F up 4.4y. Randomized to open colectomy (3 y recur 18%, 3 y OS 85%) and laparoscopic colectomy (3 y recur 16%, 3 y OS 86%, faster postoperatory recovery and 5 d stay (1 day less), less analgesics. Equivalent results.

A Govindajaran et al (JNCI2006;98:1474-81). SEER Data with N=8380 adherent CRC: 33.3% had multivisceral resection. Positive factors: age, female, SEER region, negative ly

no, and left sided tumors. Negative factors: Neoadjuvant therapy. Compared with standard resection multivisceral resection had HR=0.89 for OS without an increase in early toxicity.

E Kapiteijn et al (NEJM 2001;345:638-46). N=1.861. Randomized to Preop RT 5 Gy x 5 followed by total mesorectal excession (2 y OS 82% and 2 y local recurrence 2.4%) vs total mesorectal excission (2 y OS 81.8%, 2 y local recurr 8.2%).

A Martling et al Karolinska trial (Cancer 2001; 92:896-902). Trial 1987-1993, N=557, M F up 8.8 y, curative resection 86%. Randomized to preop RT 25 Gy in 1 wk, then 1 wk rest and then surgery (pelvic recurrence 12%, OS 46%, mortality 5% cardiovascular) vs surgery alone (pelvic recur 25%, OS 39%, mortality 1%).

R Sauer et al (NEJM 2004;351:1731-40). N=823, T3-4 &/or N+. Randomized to Preop RT 50.4 Gy/5 wk + 5FU 1000mg/m2, 120 h civi/wk 1st and 4th (5y OS 76%, local relapse 6%, Toxicity 27%) vs Postop RT similar + Boost 5.4 Gy (5 y OS 74%, local relapse 13%, toxicity 40%).

JF Bosset et al (NEJM 2006;355:1114-23). Randomized N=1011, EORTC, T3-4, respectable rectal cancer to 1) Preop RT 45 Gy (5 y local recurrence 17.1%); 2) 5FU 350 mg/m2 AF 20 mg/m2 x 5 x 2 + Preop RT (5 y loc rec 8.7%); 3) 5FU same + Preop RT + Postop 5FU x2 (5 y loc rec 7.6%); 4) RT preop + 5FU postop x 4 (5 y loc rec 9.6%). No chemotherapy was worst…

C Rödel et al (JCO 2007;25:110-7). N=110, T3-4, N+ rectal cancer treated with Preop RT 50.4 Gy/28 F + XEL 1650 mg/m2 d 1-14 & 22-35 + LOHP 50 mg/m2 d 1, 8, 22, & 28. Surgery done 4-6 wks after XEL-RT and then 4 cycles of XEL 1000 mg/m2 bid x 14 + LOHP 130 mg/m2 d 1. Results: pCR 17 (16%) + PR 53%, RO resection 95%, sphincter preservation 77%, full dose XELOX-RT 96%. Propose comparison with 5FU+RT.

T Andre et al MOSAIC Group (NEJM 2004;350:2343-51). N=2246, Stage II-III CRC, M F up 37.9 mo. Randomized study of FL alone (events 26.1% and 3 y DFS 72.9%) vs LOHP 85 mg/m2 + FL (events 21.1%, 3 y DFS 78.2%, improved results).

AB Benson III et al ASCO Recommendations for Adjuvant therapy in Stage II Colon cancer (JCO 2004;22:3408-19). No adjuvant therapy is recommended for stage II but xconsideration should be given in case of T4, inadequately sampled margins, perforation and poorly differentiated histology.

C Twelves et al (NEJM 2005;352:2696-704). Randomized study of XEL 1250 mg/m2 bid x 14 q 3 wk x 6 mo vs 5FU/FA bolus x 5d q 4 x 6. Results: HR=0.86 with a 3y DFS 64.2% and 60.6%, and also less toxicity for XEL. 3 y DFS gain 3.6%.

A de Gramont et al (JCO 2006;24:2059-64). After MOSAIC data showing FOLFOX x 4 >>LV5FU2 (4 y DFS 76% vs 70%) make a proposal of rand¡omized trial comparing FOLFOX x 4 vs FOLFOX x 4 + BV x 6 & then BV x 6 vs XELOX + BV x 6 & then BV x 6, with a total N=3000.

B Lembersky et al (JCO 2006;24:2059-64). N=1608, stage II-III , M F up 62.3 mo, (NSABBP trial). Randsomized to UFT 300 mg/m2/d + LV 90 mg/d in a tid divided dose fasting vs 5FU 1 hr after LV 500 mg/m2 in 2 h, given in 500 mg/m2 bolus wkly x 6 q 8 wk x 3. Results: Equitoxic and similar results, HR=1.01, toxicity 38%

CARCINOMA COLORECTAL- ADVANCED DISEASE CHEMOTHERAPY

S Giachetti et al HPB Villejuif (JCO 2000;18:36-47). N=200, 15 institution, randomized study comparing 5FU 700 mg/M2 + LV 300 mg/m2 at 04.00 h chronomodulated + LOHP 125 mg/m2 q 3wk (OR 53%, MPFS 8.7 mo, MST 19.9 mo) vs 5FU chronomodulated (OR 16%, MPFS 6.1 mo, MST 19.4 mo. Nodifferences found.

A de Gramont et al (JCO 2000;18:2938-47). N=420 measurable, untreated randomized to LV5fU2 alone (2 h iv LV 2oo mg/m2/d followed by 5FU bolus 400 mg/m2/d & 22 h infusion 600 mg/m2/d x 2 q 2 wk (MPFS 6.2 mo, OR 27.3%, MST 14.7 mo, Hematol toxic 5%, Diarrhea 5%) vs LV5FU2 + LOHP 85 mg/m2 2 h iv d 1 (MPFS 9 mo, OR 50.7%, MST 16.2 mo, Hematol toxic 41%, Diarrhea 12%). Benefit in first line proven.

L Saltz et al MSKCC & others (NEJM 2000;343:905-14). N=683. Randomized study comparing CPT 125 mg/m2 + 5FU 500 mg/m2 + FA 20 mg/m2 bolus wkly x 4 q 6 wks (MPFS 7 mo, OR 39%, MST 15 mo); vs 5FU 475 mg/m2 + GFA 20 mg/m2 bolus qd x 5 q 4 wk (MPFS 4.3 mo, OR 21%, MST 13 mo); vs CPT 125 mg/m2 wkly x 4 q 6 wk (MPFS 4.3 mo, OR 18%, MST 12 mo). About 75% received full doses.

P Hoff et al MDACC (JCO 2001;19:2282-92). XEL 14 d q 3wk (OR 24.8%, MTTP 4.3 mo, MST 12.5 mo) vs 5FU bolus iv qd x 5 q 4 wk (OR 15.5%, MTTP 4.7 mo, MST 13.3 mo)

JL Misset and F Levi (Sem Oncol 2000;27:78-82). 5FU infusion + FA + LOHP expected OR 50%, MST 18 mo. Chronomodulated 5FU + FA + LOHP OR 50-60% and MST 18-20 mo. Peakas of chronomodulation are LOHP 8 pm, 5FU 4 am, TXT 7 am, CPT 9 am, NVB 11 pm…

W Scheithauer et al (JCO 2001;20:165-72). Randomized study to CPT 150 mg/m2 + LOHP 85 mg/m2 q 3 wk (OR 43% and cross over 33%) vs Tomudex 3 mg/m2 (OR 19% and crossover 14%).

TS Manghan et al (Lancet 2002;359:1555-63). Randomized N=903. Lokich 300 mg/m2 qd x 21 q 4 wk (MST 302d, Mortality 2, OR 24.4%, 2 y OS 15%), vs De Gramont (5FU 400 mg/m2 bolus followed by 5FU civi 600 mg/m2 in 22 h x 2 d + FA 200 mg/m2 2h prior to 5FU) (MST 294d, Mortality 1, OR 24%) vs Tomudex (MST 266 d, Mortality 18, OR 18%).

Y Beconarn et al (JCO 2001;19:4195-201). N=62, 5FU resistant. Randomized to FUFA de Gramont + CPT alt FUFA + LOHP (MPFS 8.2 mo, MOS 9.8 mo) vs LOHP 85 mg/m2 + CPT 200 mg/M2 d 1 q 3 wk (MPFS 8.5, MOS 12.3 mo).

J Souglakos et al (JCO 2002;20:2651-7). N=31. CPT 150 mg/m2 + LOHP 65 mg/m2 + 5FU 400 mg/m2 iv bolus-600 mg/m2 civi 22 + FA 200 mg/m2 before 5FU, repeated q 2 wk. Results: CR 6.5%, PR 51.6%+ NC 25.8% + P 16.5%. MDR 9 mo, MTTP 13 mo. Highly active.

A de Gramont et al (Sem Oncol 2002;29:42-9). (3 trials). Alimta in firast line: OR 16%, MST 16 mo.

A Falcone et al (JCO 2002;20:4006-14). N=42. CPT 175 mg/m2 + LOHP 100 mg/m2 + FA 200 mg/m2 + 5FU 3800 mg/m2 civi repeated q 2 wk. Results: OR 71.4% (CR 11.9% + PR 59.5%). MPFS 10.4 mo, MOS 26.5 mo.

NH Fernando et al (Sem Oncol 2003;30:39-50). N=104 CRC. Randomized to Control 5FU/FA (OR 17%), 1 y OS 58%); BV 5 mg/kg +5FU/FA (OR 40%, 1 y OS 74%); BV 10 mg/kg + 5FU/FA (OR 24%, 1 y OS 61%).

A Grothey et al (JCO 2004;22:1209-14). Review published trials of LOHP + CPT + 5FU/FA as first line therapy and found a prolongation of survival time of 3.5 mo (over the expected 20 mo MST). Can be used to maximize the response.

L Saltz et al (JCO 2004;22:1201-8). Phase II open label clinical trial with Erbitux. N=104 with EGFR expression in formalin fixed tissue >grade 4, all failed to previous CPT. Combined CPT + Erbitux 400 mg/m2 2 h iv followed by 250 mg/m2 iv 1 h wkly. OR 9%. Acute rash 86%, asthenia 56%, no diarrhea, neutropenia. 5 OR (21 NC or mR), MST 6.4 mo. Skin rash correlated with response (grade 0 mst 2 mo; grade 1-2 MST 6.4 mo; grade 3 MST 9.5 mo).

C Turnigand (A de Gramont) (JCO 2004;22:229-37). N=220. Randomized to FOLFIRI x 6 (5FU bolus 400/m2 the 2400-3000/m2 46 h civi + FA 400 /m2 2 h iv + CPT 180/m2 2 h iv) followed by FOLFOX x 6 (MST 21.5 mo) vs FOLFOX x 6 (same 5FU + FA + LOHP 100/m2) (MST 20.6 mo). No differences, first time MST exceeds 20 mo.

H Hurwitz et al (NEJM 2004;350:2335-42). N=813 CRC untreated mets. Randomized to IFL + Placebo (MST 15.6 mo, MPFS 6.2 mo, OR 34.8%, MDR 7.1 mo, Grade 3 hypertension 2.3%) vs IFL + BV 5 mg/kg 2q 2 wk (MST 20.3 mo, MPFS 10.5 mo, OR 44.8%, MDR 10.4 mo, grade 3 hypertension 11%).

Meta-analysis group (JCO 2004;22:3766-75). 19 trials. 5FU (OR 11%, MOS 10.5 mo) vs 5FU/FA (OR 21%, MOS 11.7 mo). Better but small differences.

K Shirao et al (JCO 2004;22:3466-74) Japanese 44, Americans 45. Uracil-Tegafur + po FA: PK similar, OR 36.4% and 34.1%, Similar AUC and toxicity.

G Masi et al (Ann Oncol 2004; 15: 1766-72). FOLFOXIRI (CPT 165 mg/m2 d 1 + LOHP 85 mg/m2 d 1 + 5FU 3200 mg/m2 civi 48 h + FA 200 mg/m2 d1, repeated q 2 wks. Neutropenia 34%, diarrhea 16%, GCSF 23%, dose delivered 88%, 4 CR + 19 PR +7 NC (OR 72%), MPFS 10.8 mo, MST 28.4 mo, M F up 18.1 mo.

Q S Chung et al E Rowinski (Clin Ca Res 2004;10:4913-21). S1 (Ftorafur toxic + Uracil to inhibit DPD (components of Tegafur) + 5 chlorodihydroxy pyrimidine (DPD inhibitor x 200 uracil potency) + oxanic acid (prevent diarrhea). MRD 50 mg/m2/d x 28 q 5 wk.

D Cunningham et al (NEJM 2004;351:337-45). EGFR+ patients. Randomized to Erbitux 400/m2 then 250 /m2 wkly (OR 10.8%, MTTP 1.5 mo, MOS 6.9 mo) vs Erbitux + CPT (OR 17.5%, MTTP 4.1 mo, MOS 8.6 mo).

F Kabbinavar et al (JCO 2005;23:3706-12). Combined results from 3 studies: Randomized to 5FU/FA + BV (MST 17.9 mo, MPFS 8.8 mo, OR 34.1%) vs 5FU/FA (MST 14.6 mo, MPFS 5.6 mo, OR 24.5%). Remember that 5FU/FA + BV in third line had no effect (ASCO 2004;23:249).

HX Chen et al (JCO 2006;24:3354-60). BV + 5FU/FA 3rd line: N=350. OR 4%, MPFS 3.5 mo, MOS 9 mo…

JA Meyerhardt et al (JCO 2006;24:1892-7). Phase II N=32. Tarceva 150 mg po qd + XEL 1000 mg/m2 bid d 1-14 + LOHP 130 mg/m2 d 1, repeat q 3 wk: Results: OR 8/32 PR + 14/32 NC. MPFS 5.4 mo, MOS 14.7 mo.

R Goldberg et al (JCO 2006;24:3347-53). N=305. Randomized to Reduced IFL (decreased 20%, CPT 100-F400-FA 20 d 1, 8, 15, 22 q 6 wk) (TTP 5.5 mo, OR 32%) vs FOLFOX4 (LOHP 85-400/600 xcivi d 1, 2, repeat q 2 wk) (TTP 9.7 mo, OR 48%).

H Hochter (Sem Oncol 2006;33:S8-S14). First line Chx: Pilot trial of IFL+BV improved OR 15% and OS 5 mo, then FOLFOX/FOLFIRI followed +/- BV also improved 20% OR and 5-7 mo PFS, not OS. Then Vatalanib (PTK787) showed no benefit combined to FOLFOX. BV is active and hypertension can be controlled. Stop BV if uncontrolled hypertension or proteinuria (> 2g/24 h), stop also if thromboembolism (prior TE is not a contraindication since low dose ASA might prevent it), contraindicate BV in case of bleeding, surgical wound or GI perforation.

CARCINOMA COLORECTAL- IMMUNETHERAPY

S Welt et al (Clin a Res 2003;9:1338-46). Phase I huA33, 10-50 mg/m2/wk, in patients with CHx tresistant CRC. HAHA 8/11. OR 1 (1/3 without HAHA), NC 4 (with CEA reduction). Immunogenic...

S Welt et al MSKCC (Clin Ca Res 2003;9:1347-53). HuA33 wkly x 14 + BCNU + 5FU + VCR + STREPTOZ. N=12 heavily pretreated. 7/12 HAHA. OR: 3 PR + 1 mR. Surprise...

S Matsumoto et al (Br J Ca 2002;86:161-7). N=64. CRC after surgery, randomized to Cimetidine (10 y OS Stage C 84.6%, Stages A&B 90.5%, Ca19.9+90.9%) vs control (Stage C 23.1%, A&B 69.5%, Ca19.9+20.1%). Cimetidine inhibits binding endothelial cell

adhesionand inhibits T-cell suppressors). (Active in patients with high sLx and sLa antigens) (Cimetidine increases TIL when given preoperatively, Nat Med 1:1243-4, 1995). (Cimetidine modulates dendritic cell differentiation , T Kubota et al BJC 2002;86:1257-6)

G Uelenhag et al (Clin Ca Res 2004;10:3273-81). CEA vaccine (recombinant) + GM-CSF 80 ug/d x 4d x 4 in 1 y. Results: 12/12 developed T cell response (H3 thymidine incorporation) & IgG response (ELISA); 9/12 with CEA alone T cell & 8/12 IgG response. Responses persisted > 1y.

V Mazzaferro et al (Clin Ca Res 2003;9:3235-45) Vaccination after liver resection for metastasic CRC, with autologous HSP-Gp96, 4 wkly, the 2 biweekly after 8 wks, intradermal vaccine rotating, measured effect by ELISPOT. N=29. OR: T cell mediated 15/29 (52%), CD3+, CD45Ra+, CCR7-. Increased 2y OS 89% vs 64% and 2 yDFS 46% vs 18%, according to response.

A Scott et al (Clin Ca Res 2005;11:4810-7). HuA33 (A33Ag glycoprotein 43 kDa, IgG superfamily) in animals: long retention in tumor, high uptake and minimal GI toxicity. Phase I: 12 patients with liver metastases, doses 0.25-10 mg/m2. Selective and rapid localization. I131-huA33 uptake excellent, t1/2 Beta= 86 h, Tumor/normal tissue=16.3, No antibosdy responses in 4 patients.

G Chong et al (Clin Ca Res 2005;11:4818-25). N=15. HuA33-I131 therapy labeling and then therapeutic dose 20-50 mCi/m2. MTD 40 mCi/m2 (thrombopenia at 50 mCi/m2). 4 developed antibodies: 4 NC and 11 PD. Recommend combination with chemotherapy.

T Liersch et al D Goldenberg (JCO 2005;23:6763-70). N=23 liver mets, M F up 64 mo. RAIT after surgery of liver mets with I131-Labentuzumab (antiCEA) 40-60 mCi/m2: MOS 68 mo, MDFS 18 mo, 5 y OS 51.3%.

R Harrop et al (Clin Ca Res 2006;12:3416-24). Vaccinia Ankara virus (attenuated) encoding antigen 5T4 (Trovax). N=22 mets CRC. TROVAX 5x10e7-5x10e8 PFU at 0, 4 and 8 wk. 16/17 specific cellular response and 14/17 detectable antibodies. 5 NC after 3-18 mo, correlated with Ab response. No autoimmunity.

CARCINOMA COLORECTAL- PERITONEAL THERAPY

O Glehen et al Lyon (JCO 2004;22:3284-92). Cytoreductive surgery + intraoperative chemotherapy, multi-center trial. N=506, 28 institutions, median age 51 yo, median F up 53 mo. Results: MOS 19.2 mo, CR surgery MST 32.4 mo. IP Drugs MitoC +/- CDDP, LOHP + early postop 5FU +/- MitoC. 3 y OS 30%.

DM Elias IGR (Ann Oncol 2004;15:781-5). Sugarbaker + (1 h before LOHP, 5FU 400 mg/m2 + FA 20 mg/m2) LOHP-hyperthermia 460 mg/m2 in 2 l/m2, 30 min at 43ºC at flow rate 2l/min. N=124, M F up 27 mo. Sugarbaker index 16.99.5, MT surgery 490 min, M

blood loss 965 mL.8% postop deaths (ACV) morbidity gr 2-3=37.5%. 3 yOS 65%, 3yDFS 50%, Only 32% had peritoneal recurrence (Peritoneal recurrence with index <24 = 17% only)

CARCINOMA COLORECTAL- LIVER METASTASES

NCCN Guidelines for liver metastasectomy: Prior laparoscopic examination: ly no+ in primary, relapse free interval <12 mo, >1 liver mets in preoperative study, CEA>200 ng/ml 1 mo after surgery, largest tumor>5 cm. Contraindications: extensive unresectable extrahepatic disease, involvement of hepatic artery-major bile ducts-portal vein, >70% liver invoplvement or >6 segments or 3 hepatic veins and no adequate postresection hepatic reserve.

M Lorenz et al (JCO 2000;18:243-54) N=168, 25 centers. Randomized to 5FU/FA (HAI) (MTTP 9.2 mo, MST 18.7 mo); vs 5FU/FA iv (MTTP 6.6 mo, MST 17.6 mo), and 5FUDR (HAI) (MTTP 5.9 mo, MST 12.7 mo).

W Kern et al (Ann Oncol 2001;12:599-603). N=21. LOHP IA 125 mg/m2 q 3 wk (4 h infusion) + FA 200 mg/m2 1 h + 5FU 600 mg/m2 in 2 h. Results: OR 59%. MTD 150 mg/m2 LOHP.

M Lorenz et al (Ann Oncol 2001;12:321-5). Wkly IA 5FU 24 h MRD 2200 mg/m2. N=50. OR 56% + NC 26%. MPFS 12 mo, MOS 22.3 mo, active… Intraarterial port device.

B Gray et al Royal Perth Hosp West Australia (An Oncol 2001;12:1711-20). Randomized study comparing HAI 5FUDR 0.3 mg/kg x 12 d (OR 17.6%, CEA 47%, MTTP 7.6 mo, 3 y OS 17%, MST 12 mo) vs 5FUDR + SIR spheres Y90 (2-3 GBq) (OR 44%, CEA 72%, MTTP 12 mo, 1 y OS 72%, 3 y OS 6.5%, MST 18 mo).

N Kemeny et al ECOG (JCO 2002; 20:1499-505). 1-3 resectable liver ,mets randomized after surgery to control (eval 45/56, 4 y RFS 25%, MST 49 mo, MOS 47 mo, 4 y OS 52.7%) vs HAI FUDR 0.2 mg/kg x 14 + 5FU civi 200 mg/m2 x 14 d q 4 wk (4 yRFS 46%, MST 63.7 mo, MOS 34 mo, 4 y OS 61.5%).

D Weinreich et al HR Alexander, NIH (Sem Oncol 2002;29:136-44). Hepatic perfusion with hyperthermia in 7 patients resistant to HAI: 5 OR (71%) and MPFS 10 mo, MOS 19 mo. Percutaneous device HP (Delcath Systems Inc, Stanford, CT).

S Sadahiro et al (Cancer 2004;100:590-7)
N=316, stage ii-III, complete surgery, M F up 59 mo. Randomized prophylactic HAI (5FU 250 mg/d x 3 wk vs control. Recurrence risk 0.4, Death ris 0.37, Liver mets risk 0.38. (3 y DFS 88% vs 72%, 5 y DFS 86% vs 68%, 3 y liver free OS 94% vs 79%.

B van Etten et al (A Eggermont) (Ann Surg Oncol 2004;11:558-605). Isolated perfusion for liver mets, balloon catéter isolated hypoxic perfusion technique. N=18. OR 12%, MTTP 4.8 mo. Leakage 56%.

R Alexander et al (JCO 2005; 23:3465-74). N=28, 74 procedures. Hepatic artery LPAM escalated dose, MRD 3 mg/kg. OR 30% (ocular melanoma OR 50%). Grade 3-4 liver toxicity transient 19%, grade 3-4 systemic toxicity 66%.

Mfaynsod et al (JCO 2005;23:4876-80). FUDR portal vein infusion adjuvant therapy after surgery of liver metastases (sequential, alternating or concurrent regional FUDR/systemic 5FU/FA). N=51, median mets 3 (range 1-11). Completed treatment 55% at >75% doses). 1 y OS 92.7%, 3 y OS 41.8%, 1 y DFS 64%, 3 y DFS 19%, recurrence in the liver 36%.

M Ducreux et al (JCO 21005;23:4881-7). HAI LOHP 100 mg/m2 + iv LV5FU2. N=28, M F up 23 mo, median tretament 8 cycles. OR 64%. MOS 27 mo, MDFS 27 mo

N Kemeny et al (JCO 2005;23:4888-96). N=36. Group A: HAI FUDR 0.12 mg/kg + system LOHP 100/m2 + system CPT 150 mg/m2; Geroup B: iv LOHP 100mg/m2 + iv 5FU 1400 mg/m2 civi 48 h /FA 400 mgM2x 30 ml + HAI FUDR. Results: OR 88%. Diarrhea 24%, neutrropenia <10%, neurotoxicity 20%, bilirubin 6%. MST 36 mo Group A & 22 mo Group B. 7 patients in gropu A underwent surgical resection.

N Kemeny et al (JCO 2006; 24:1395-403). Randomized study comparing HAI (FUDR 0.18 mg-kg-30 mL-day +LV 4 mg/m2+ DXMTS 25 mg + heparin 30000 in a 14 d civi/14 d rest (MOS 24.4 mo, OR 47%, TTP liver 9.8 mo) vs FA 20 mg/m2 then 5FU 425 mg/M2 bolus qd x 5 q 4 wk (MOS 2º mo, OR 24%, TTP liver 7.3 mo) . Hematolog toxicity better HAI (0 % vs24%)& liver toxicity worst HAI (18% vs 0%). Results: Better HAI.

E Berber et al (JCO 2005;23:1358-64). N=135, liver mets. Laparoscopic RFA. Factors of survival: largest tumor < 3 cm, CEA <200 ng/ml., 1-3 tumors. MOS 28.9 mo (historical obtained with chemotherapy 11-14 mo).

P Sugarbaker (Sem Oncol 2005;32:S68-S73). Total 333 pts and 28% 3 y OS. In different series 3 y OS 18-47%. Figures compare to liver resection and never was done a randomized trial confirmatory study to make it an acceptable procedure.