Results: TA+ tumors are 61% of 305 specimens. There was a statistical significant correlation only between TA and pN, G, and MIB1 value (see table).

Conclusions: In invasive breast cancer TA is significantly associated with nodal metastasis, cellular proliferation (Ki67/MIB1) and histological grade. The correlation between TA and clinical outcome are under evaluation.

1000 ORAL

Expression profiling predicts poor outcome of disease in young breast cancer patients

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Purpose: Twenty percent of lymph-node negative breast cancer patients diagnosed at young age develops distant metastases at 5 years follow-up. We used expression profiling of the primary tumor for diagnostic classification and identification of an expression signature predictive for distant metastasis.

Methods: RNA of 97 breast tumors of LN0 patients (age < 55 yrs) with known clinical outcome was profiled on DNA microarrays that represent ~25,000 human genes fabricated with an ink-jet oligonucleotide synthesizer.

Results: Two-dimensional clustering displays two distinctive types of tumors based on differential expression of ~5100 genes. Discriminant and statistical analyses revealed sets of reporter genes for diagnostic subtypes, e.g. related to BRCA1 status (~300 genes). An expression signature for prediction of early distant metastasis was established (83% correct classification) and its predictive power was confirmed on an independent set of 19 tumors. In a multivariate model including known clinical parameters (logistic regression) the expression profile is a strong determinant of prognosis ($p < 0.001$).

Conclusion: Expression profiling is a powerful diagnostic tool in breast cancer and allows 'array-guided' tailored therapy.

Colo-rectal cancer

1001 ORAL

Continuous vs intermittant chemotherapy for advanced colorectal cancer: preliminary results of the MRC cr06b randomised trial

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A survey of UK clinicians suggested that there was no consistent policy regarding the duration of treatment for patients receiving chemotherapy for advanced colorectal cancer. Patients who were responding or had stable disease after receiving 12 weeks of de Gramont, Lokich or Raltitrexed therapy were therefore randomised to either 'continue' therapy until progression, or 'stop', re-starting on the same therapy on progression. The trial was closed in August 2000, when 354 patients had been entered from 42 UK centres in 4 years. Median age of patients was 64 years, 64% were male, 86% were WHO PS Grade 0/1, 65% had colon cancer, and 40% had responding disease, and these characteristics were well-balanced between the two policies. Of the 178 patients allocated to 'stop', 39% re-started treatment after a median of 134 days, mainly due to disease progression. Median time on re-started treatment was 83 days. The 'continue' group remained on treatment for a median of a further 91 days, stopping for progression (44%), toxicity (15%), or clinician or patient decision (35%). Similar proportions of patients on both groups received second-line therapy. Patients on 'continue' experienced significantly more serious adverse events and toxicity, and using patient-assessed EORTC QLQ-C30 and HADS reported significantly worse quality of life. There was no clear evidence of a difference in progression-free survival (HR 1.16 95% CIs 0.92-1.45, p=0.21) or overall survival (HR 0.87 95% CIs 0.68-1.12, p=0.28). From randomisation (after an initial 12 weeks of chemotherapy), median, and estimated 2-year survival were 11.8 and 11.2 months, and 18% and 14% for 'stop' and 'continue' respectively. The result of this trial, that there is no clear evidence of a benefit in continuing therapy indefinitely, and that there appears to be a gain in QL for the 'stop' policy, provides an evidence-base for stopping chemotherapy after 12 weeks

1002 ORAL

5-FU-based adjuvant chemotherapy given after neoadjuvant chemoradiation and surgery for rectal cancer improves survival only among responders

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Purpose: To analyze the influence of adjuvant 5-FU-based chemotherapy (ADJ-CTX) on survival in rectal cancer patients treated with preoperative chemoradiation (CXRT) and surgery.

Materials and Methods: From 1990 to 1998, a total of 318 patients with Stage II-III rectal cancer were treated with CXRT followed by surgery with or without ADJ-CTX. CXRT (45 Gy/25fx with protracted venous infusion, 5-FU 300mg/m2) was delivered to 97% of patients (311/320). Patients were resected 4-6 weeks later. ADJ-CTX consisted of 5-FU and leucovorin for 4-6 cycles and was given in 181 patients (57%). Kaplan-Meier univariate and Cox Regression mutivariate methodology was used to evaluate survival.

Results: Median follow up was 59 months for living patients. Objective evidence of tumor response indicated by T-stage downstaging (TSD) occurred in 51% (161/318) of cases. ADJ-CTX was given in 48% (77/161) of TSD+ and 38% (60/157) of TSD- cases, respectively. On univariate analysis of all patients, age, gender, tumor length, clinical N-stage, and distance from the anal verge were not significant, whereas circumferential involvement (p=0.01), and high grade (p=0.02) were significant. Tumor fixation (p=0.07), T-stage (p=0.065), and ADJ-CTX (p=0.092) were borderline. None were independently significant on multivariate analysis. In every multivariate model that was attempted separately in the TSD+ and TSD- groups, ADJ-CTX was the only independently significant factor in the TSD+ group (p=0,044). Nothing was ever independently significant in the TSD- group, including ADJ-CTX. The 5-year actuarial survival for TSD+ patients who received ADJ-CTX was 94% verses 81% for those who did not.

Conclusions: In this large population of rectal cancer patients treated with neoadjuvant CXRT, post-operative adjuvant 5-FU-based chemotherapy did not independently improve survival in all patients. However, it independently improved survival in the subset of patients who responded to neoadjuvant therapy (TSD+), but not in those who did not respond (TSD-). The prospective investigation of novel adjuvant chemotherapy regimens is appropriate in patients who don't respond to neoadjuvant therapy.

1003 ORAL

Definition of genetic instability as prognostic factor in colorectal cancer by microsatellite analysis and immunohistochemistry of an archival collection of patients. Comparison between sporadic and familial cases

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Background: Association between microsatellite instability (MSI) and favourable postoperative survival in patients with colorectal cancer (CRC) has been indicated. To confirm a prognostic role of MSI, we started screening a series of archival CRCs.

Patients and Methods: To date, DNA from paraffin-embedded paired samples of tumors and corresponding normal tissues from 369 CRC patients at various stages of disease was isolated. Patients [median age, 54 (range 22-90); male/female, 207/162] were surgically treated from 1987 to 2000, and disease stage recorded according to Dukes classification. PCR-based MSI analysis was performed using five microsatellite markers. Tumors were classified as MSI+ when > 2 markers were unstable. Involvement of the mismatch repair genes was evaluated by immunohistochemistry (IHC) using anti-MLH1 and anti-MSH2 antibodies on MSI+ tumor tissues.

Results and Conclusion: Among the 294 patients analyzed (March 2001), we found a similar distribution of the 95 (32%) MSI+ cases across the different disease stages (ranging from 31% of Dukes A to 34% of Dukes C cases), whereas a prevalence of MSI was observed for tumors of the right colon (20/34; 59%) in comparison to those of other sites [remaining colon (20/65; 31%) or rectum (55/195; 28%)]. Among the 174 patients whose family history was investigated, we found 11 (65%) MSI+ cases out of 17 familial CRC (> 3 affected members) versus 38/157 (24%)