Symposia

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Polygenic inheritance of predisposition to lung cancer in experimental models

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Purpose: Dissection of genetics of the complex inheritance of susceptibility and resistance to lung cancer.

Methods: Genetic linkage experiments using crosses by mouse inbred strains with inherited predisposition ant resistance to lung cancer.

Results: We have previously mapped a major locus *(Pulmonary adenoma susceptibility 1, Pas1)* affecting inherited predisposition to lung cancer in mice on chromosome 6, near *Kras2* (*Nature Genet.*, 3: 132–136, 1993). Appropriate crosses that include *Pas1*/+ mice provide a model system for identifying loci that can modify the lung cancer predisposition phenotype caused by *Pas1*. Using this approach we have mapped, on mouse chromosome 11, the *Pulmonary adenoma resistance J (Par1)* locus that selectively inhibits lung tumor development in *Pas1*/+ animals and behaves, therefore, like a modulator gene of *Pas1* (*Nature Genet.*, 12: 455–457, 1996). More recently, we and another group mapped a second lung tumor resistance locus (*Par2*) on chromosome 18, near the *Dcc* gene.

Conclusion: Experimental models provide an essential tool for the mapping of lung cancer susceptibility/resistance genes and for the subsequent cloning of candidate genes.

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Molecular intervention in small cell lung cancer

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In vitro and *in vivo* studies suggest the epithelial glycoprotein-2 to be the optimal surface protein for the development of targeted therapy in small cell lung cancer (SCLC). A recombinant immunotoxin based on a single chain fragment of antibody MOC-31 and the domains II and IIII of *Pseudomonas* exotoxin was developed by rational engineering. The current results suggest this recombinant immunotoxin to be more efficient against SCLC cells than a chemical immunotoxin based on the entire antibody.

bcl-2 overexpression is prevalent in SCLC. For functional studies, a series of antisense oligonucleotides to *bcl-2* were synthesized. The oligonucleotide 2009 targeting the coding region of bcl-2 specifically reduced the viability of SCLC cell lines over 90% and acted synergistically with doxorubicin. Our results demonstrate that bcl-2 is a life sustaining factor for small cell lung cancer and suggest that antisense to bcl-2 may have a therapeutic potential for this tumor.

Human CD24 is a glycosylphosphatidylinositol-linked surface protein overexpressed in SCLC. It is involved in cellular adhesion (ligand of P-selectin) and signalling of SCLC cells. We investigated the 5′-flanking region of the human CD24 gene for its promoter activity in lung cancer cell lines using a luciferase reporter gene. Strong and selective activity under the CD24 promoter was seen in SCLC, but not in non-small cell lung cancer. The CD24 promoter might thus serve as tool for the cell type-specific expression of therapeutic genes in SCLC.

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Genetic susceptibility linked with rare HA-ras1 alleles and microsatellite alterations in non-small cell lung cancer (NSCLC)

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Purpose: Rare alleles of the H-ras1 minisatellite have been linked to increased susceptibilty to several neoplasms including NSCLC. We searched for rare H-ras1 alleles in peripheral blood lymphocyte DNA and in fresh tumors corresponding to 88 alleles from 44 resected NSCLC patients (pts) and 306 alleles from 153 healthy controls by PCR assay.

Method: Amplified products were electrophoresed through 40 cm long, 1.2% agarose gel. We also searched for the presence of microsatellite alterations using 3 dinucleotide markers on chromosome 3p (D3S1038, D3S1289, D3S1284) and one GAG trinucleotide on chomosome X.

Results: We found a higher number of rare alleles in NSCLC pts, 18/88 (20.4%) in contrast to the control group, 40/306 (13%). Among the rare alleles, al+4 was the most prevalent in 44% of NSCLCs. Loss of heterozygosity (LOH) was 31% and was more frequently observed (86%) in the NSCLC group with common Ha-ras1 alleles.

Conclusion: Rare Ha-ras1 alleles and LOH on chromosome 3p define divergent pathways in the development of NSCLC. Furthermore, rare Ha-ras1 alleles screened from blood DNA could plausibly represent an easy tool for use during the follow-up of resected NSCLC pts.

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The results of the accelarated fractionation scheme chart in the treatment of non-small cell lung cancer

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The knowledge that tumours have a potential for rapid cell proliferation has led to the hypothesis that tumours may repopulate during a course of radiotherapy. This led to the investigation of accelerated radiotherapy regimes. CHART (Continuous, Hyperfractionated Accelerated Radiotherapy) is the most accelerated regimen in clinical practice: 54Gy is given in 36 fractions of 1.5Gy treating three times per day for 12 consecutive days inclusive of the weekends.

A multicentre randomised controlled trial has been carried out under the auspices of the CHART Steering Committee comparing CHART to conventional radiotherapy 60Gy in 6 weeks in non-small cell carcinoma of the lung. A total of 563 patients were entered by 13 centre between April 1990 and March 1995. Patients with non-small cell lung cancer localised to the chest with a performance status of 0 or 1 were included.

The groups were well matched with regard to prognotic factors. Overall there was a 24% reduction in the relative risk of death equivalent to an absolute improvement in 2 year survival of 9% from 20 to 29% ($p = 0.004$). Likewise there was a significant improvement in local tumour control ($p = 0.027$).

CHART gave a significant improvement in survival in non-small cell lung cancer when compared to conventional radiotherapy. Further improvement may be achieved with dose escalation using conformal therapy, hypoxic cell radiosensitisation and/or by the addition of cytotoxic chemotherapy.

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Combined chemotherapy and radiation

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The efficacy of radiation in locally advanced NSCLC is limited. In a search for improving the outcome, particular attention has focused on the possibility of adding chemotherapy to radiation. The major expectation from this approach has been to increase the cure rate by either improved locoregional tumor control or by elimination of micrometastases outside the radiotherapy field. Two most frequently used strategies include chemotherapy preceding radiation and concurrent application of both modalities. The results of phase III trials comparing radiation alone to radiation combined with chemotherapy have been equivocal. Early studies utilizing chemotherapy not containing cisplatin were usually negative. More recent use of cisplatin-based regimens particularly if applied as *induction* treatment, has been found to produce modest, but significant survival benefit. The role of *concurrent* radiother-

apy and cisplatin (believed to be a radiosensitizing agent) is controversial. Improved local control and survival from adding this compound to radiation has been demonstrated in one study, but at least two others studies were negative. The interpretation of many studies is difficult due to small patient samples and methodological flaws. It may be concluded therefore that chemotherapy may have a role as an adjunct to radiation in locally advanced NSCLC, but the gain from this approach should be weighted against increased early and late toxicity. Moreover, improvement of similar magnitude has been achieved with the use of modified radiotherapy techniques (hyperfractionation, CHART). A possible benefit from combined modality treatment should therefore be confirmed in further research.

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Non-small cell lung cancer: How extensive should surgery be?

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Objective: Surgery is the treatment of choice in stage I and II bronchial carcinoma (BC). In stage III with extrapulmonal structures/organs involved, however, operative treatment is discussed controversially. Involvement of peripheral and mediastinal structures requires extensive interventions, e.g. mediastinal lymph node dissection and/or broncho- and angioplastic procedures.

Material and Methods: 6907 patients with BC, admitted to our institution between 1984 and 1994, were analysed. 2464 patients (36%) were resected.

Results: R_0-resection was achieved in 1996 patients, including 454 cases of BC stage IIIA, and 323 cases of BC stage IIIB. R_0-resection rates were 81% and 58%, respectively. 5-yr-survival was 26% in stage IIIA and 19% in IIIB. 5-yr-survival rates vary in correlation to spread of lymph node metastases, in case of stage IIIA between 39% and 14%. Stage IIIB collectives showed 5-yr-survival rates between 24% and 14%, respectively. Mediastinal lymph node involvement, therefore, appears to be a relevant prognostic factor. 30-day-mortality for all R_0-resected stage III tumours was 9%.

Conclusions: Surgery in BC stage III offers potential cure after complete resection. Adequate surgical management necessarily encompasses technically complicated procedures. A close interdisciplinary cooperation is required.

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New drugs and their possible impact on patient outcome

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CPT-11 is a semi-synthetic water soluble derivative of camptothecin. It is administered at the dose of 350 mg/sqm every 3 weeks (wks). Overall 455 patients (pts) have been treated in phase II studies. The response rate (RR) was 12.9%, stable disease (SD) 42%. Overall median survival (ms) was 9 months (mts), 14.5 for partial (P) R and 12.5 for SD. 61% of pts with PR or SD had pain relief attributable to CPT-11. Toxicity include short lasting neutropenia, early and delayed diarrhea (dd), nausea (n), vomiting (v), hair loss, fatigue. dd was significantly reduced with prompt administration of loperamide and antibiotics starting after 24 hrs if dd was not resolved.

Tomudex is a specific TS inhibitor administered at the dose of 3 mg/sqm every 3 wks. Compared to 5FU/folinic acid (FA) regimen in 3 large randomised studies, RR and toxicities were comparable. Improved PS and weight gain was demonstrated in both arms. Overall ms was comparable in 2 trials and superior for 5FU/FA in one.

Oxaliplatin is a non-nephrotoxic third generation platinum complex. It is given at the dose of 130 mg/sqm over 2 hrs in 5% glucose every 3 wks. Dose-limiting toxicity is a peripheral dysesthesia aggravated by cold. It has been investigated, mainly, in combination with continuous infusion of 5FU. RR of 50% to 28% have been reported for 1st and 2nd line treatment respectively. ms was 16 and 12 mts. 20 to 30% of pts with liver and lung metastases could be reoperated with a curative aim. New agents with various mechanism of action provide reason for optimism regarding the management of pts with advanced disease.

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Intense local therapy in resectable rectal cancer

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Purpose: To describe methodology and results in rectal cancer combining preoperative chemoradiation, radical surgical resection and intraoperative electron irradiation (IORT).

Methods & Materials: From 8/95 to 6/96 76 patients with localized rectal cancer were treated with preoperative irradiation (40–50 Gy), simultaneous 5FU iv ci (500–1000 mg/m2) +/– CBDCA 55 mg iv, d 1–4/21–24 of radiotherapy. Radical surgery was performed 4–6 weeks after the completion of the neoadjuvant segment. IORT electron boost was added to the presacral space (10–15 Gy) after tumor resection. Adjuvant chemotherapy using 5FU-LV was recommended to patients with B2-C tumor downstage. Pretreatment clinical findings showed: mobile disease (9%), tethered (49%) and fixation (42%).

Results: Tolerance to the treatment program was acceptable. Pathologic tumor downstaging identifed 25% of pT_0/pTmic surgical specimens. With a median follow-up of 24 months (range +3 to +99 months) patterns of tumor progresion has shown 1 mixed recurrence (anastomotic site + lung) and 9 systemic failures. Actuarial cause specific survival is projected 72% at 8 years.

Conclusion: Intense local therapy is feasible in resectable rectal cancer patients in the context of an expert group in IORT and chemoradiation. Pelvic failure has been eradicated (presacral IORT boosted region). Tolerance to the integral treatment intensity was acceptable. Up dated results to May 97 will be presented.

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Frontiers in the management of colorectal cancer – Combined modality treatment

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Even after apparently curative surgery for colorectal cancer, microscopic deposits are frequently left. These deposits, each containing between 10^6–10^8 cells may be eradicated by radiotherapy, chemotherapy or immunotherapy resulting in improved disease-free and overall survival. Radiotherapy is the most effective modality, potentially killing 10^6–10^8 cells if the doses are sufficiently high but is limited to a region such as the pelvic cavity in rectal cancer. Preoperative radiotherapy, being more dose-efficient than postoperative, has also reduced local failure rates and improved survival. Chemotherapy has limited cell kill effects, but has yet improved survival to a limited but clinically relevant extent in colon Dukes' C. The relative benefits may be as large also in Dukes' stage, but the absolute gains are then much less due to fewer recurrences and the routine use of the additional treatment is then questionable. Both radiotherapy and chemotherapy may have acute and late adverse effects. Inappropriate techniques, such as used in certain radiotherapy trials, have also caused both acute and late effects, at least partly counterbalancing the positive effects. Each modality must be used in an optimized way. This also relates to the surgery. If the surgical techniques are optimized, such as they could be in rectal cancer, the relative gains by for example preoperative radiotherapy may not change, or they may even increase, but the absolute gains, and thus cost-effectiveness, may decrease. A review of recent results from controlled clinical trials will be made and directions for future improvements in outcome presented.

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To 5-FU or not to 5-FU? When, how and why to use the new active agents in advanced colorectal cancer

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Patient characteristics, disease history and pretreatment characteristics should be determinant in the choice of systemic treatment in ACRC. The availability of modern imaging and reliable markers should be fully exploited now that a surge in surgical enthusiasm and molecular pharmacology tumor markers: p53, thymidilate synthase, mismatch repair defects, ADCC presence are put forward as putative natural history and treatment dependant pronostic factors. New thymidilate synthase active drugs, CPT-11 and Oxaliplatin have proven viable alternatives to 5-FU. The current prevalence of previous adjuvant treatment in metastatic disease populations and the simultaneous availability of new active agents are opportunities not to