these decisions become somewhat easier once genetic testing becomes available.

As far as interventions that might be employed prophylactic mastectomy would only be considered for these extreme cases and even this intervention cannot guarantee 100% protection. Mammographic screening for the pre-menopausal women where the familial predisposition tends to express itself is of unproven value.

Finally a good prospect for intervention for familial predisposition to breast cancer would be chemoprophylaxis. Trials of tamoxifen are currently under way but these may be more appropriate to post-menopausal women. For the pre-menopausal women I am of the opinion that we will one day be able to develop a safe and effective contraceptive regimen that will incidentally reduce the risk of breast cancer.

324
NO ABSTRACT

325
NO ABSTRACT

326
NEW STRATEGIES FOR PREVENTION OF COLON CANCER—PARADIGM: FAMILIAR POLYPOSIS COLI, HEREDITARY NONPOLYPOID COLON CANCER (HNPCC) AND ULCERATIVE COLITIS

Ch. Herfarth, J. Gebert, M. Kadmon, M. v. Knebel-Doeberitz
Department of Surgery, University of Heidelberg, 69120 Heidelberg, Germany

Familial colorectal cancer can be divided into two distinct classes, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Identification of gene loci assigned to FAP (APC gene) and HNPCC (mismatch repair genes) has allowed molecular analyses of affected patients as well as individuals at risk within those families. We established a presymptomatic molecular diagnosis for FAP families registered at our hospital. Since the majority of mutations identified to date lead to truncated proteins we used a non-radio-active protein truncation test (PTT) as a screening method. According to this assay five overlapping segments of the APC coding sequence were amplified by PCR and subsequently transcribed and translated *in vitro* in a rabbit reticulocyte lysate using biotinylated t-RNA Lys. Labelled proteins were separated by PAGE, transferred to nylon membranes, and detected by streptavidin-alkaline phosphatase complex in a colour reaction.

We have started analyzing HNPCC patients at the molecular level. Selection of patients was not based on strict Amsterdam criteria but rather on early age of onset of disease (<50 years) or anamnestic criteria. Seven colorectal cancer patients—three of them matching the Amsterdam criteria—were analyzed for mutations within the complete coding sequence of the hMutS2 mismatch repair gene by PTT and direct sequencing. No mutations were found although microsatellite instabilities could be demonstrated in three patients. Since microsatellite instabilities are indicative of replication error caused by a defective mismatch repair system our future sequence analyses will be extended to the other known mismatch repair genes.

While in the 80's we still considered the subtotal colectomy and ileorectal anastomosis in FAP as a good alternative to a restorative proctocolectomy in cases of few rectal polyps, we nowadays almost exclusively perform a mucosal proctectomy and ileal pouch-anal anastomosis with equal functional results. Even singular polyps in the rectum are for us a reason to go for this far more radical and safe procedure from the oncological point of view. And we are reinforced by our longterm experience with subtotal colectomies requiring secondary surgery or even developing metachronous rectal cancer despite close follow-up of the rectum.

327
CHOICE OF TREATMENT IN MEN SYNDROMES

L.E. Tisell
Department of Surgery, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden

Multiple Endocrine Neoplasia syndromes are genetic diseases with autosomal dominant inheritance. There are three such syndromes. The MEN type 1 syndrome is characterized by hyperparathyroidism, pancreatic islets tumors, and pituitary adenomas. The genetic defect has been mapped to chromosome 11. The MEN type 2A syndrome includes hyperparathyroidism, medullary thyroid carcinoma and pheochromocytoma(s). The MEN type 2B syndrome includes medullary thyroid carcinoma and pheochromocytoma(s) but also ganglio-neuromas of the gastrointestinal tract. The inherited defects responsible for the MEN2 syndromes map to the pericentromeric region of chromosome 10. Hormonal screening of members of MEN families have led to earlier diagnosis and treatment. This has improved the quality of life and the survival. In our experience the patients with MEN 2A syndromes have the same survival as the normal population. The introduction of genetic diagnosis will further improve the outcome of treatment for these patients.

328
APPROACHES TO LOCAL RECURRENCES AND METASTATIC CANCER

A. Gentil Martins
Department of Pediatric Oncology, Inst. Port. Oncologia de F. Gentil e Depart. Surgery, H. D. Estefânia, Lisboa, Portugal

Surgery of Local Recurrences is conditioned by the "radicality of previous surgery, the likelihood of total ressection, the histological type, the response to chemotherapy, prognoses, sensitivity to radiotherapy and absence of metastatic lesions (unless those are amenable to surgical ressection). Surgery for metastatic cancer implies that all metastatic lesions can be excised and the primitive tumour is or can be controlled.

In both cases a good general health of the patient is a prerequisite for surgery of recurrence or metastases. The most difficult decision is option between "radical" treatment or just paliation, in order not to jeopardize the quality of life of the patient during his remaining life span. Several examples are presented, from abstention to radical surgery. Treatment must be individualized and take into account previous treatments, probability of response to alternative treatment methods and overall prognoses. If the above criteria are respected, surgery remains an essential step for the cure of recurrent or metastatic solid tumours in children.

329
THERAPEUTICAL PHILOSOPHY OF SECUNDARITIES IN CHILDREN WITH SOLID TUMOURS

J. Koutecký[1], J. Šnajdauf[2]
[1] Department of Paediatric Oncology
[2] Department of Paediatric Surgery, 2nd Medical Faculty of Charles University, Prague and University Hospital Motol, Prague 150 18 Prague 5, Czech Republic

After years of experience, every responsible oncologist has to create a personal oncologic philosophy/and therefore a personal philosophy of his or her professional and moral accomplishment/which allows orientation in problems of the field. Using the professional philosophy it is possible to search for and find the principles, structure and form of scientific knowledge. This way it is also possible to analyse techniques and methods of the field, to derive and justify scientific findings linked to their development, and to establish strategies of scientific and research programmes. Without such a personal philosophy one cannot make decisions about therapy of life-threatening childhood diseases recidives and metastates of tumours being good examples of this. A wise equilibrium among all substantial circumstances—i.e., study of the disease, complex medical status of the patient, the physician's attitude and abilities, scientifically approved therapeutic choices, their limits and ethical principles—is the only possible alternative now as well as a ground for the future. The lecture indicates the aforementioned direction.

330
SURGERY OF LUNG METASTASES

A. Vos

Background: A retrospective analysis was performed of the results of surgical excision of lung metastases in children to identify prognostic factors.

Methods: From 1970 to 1992 139 thoracotomies were performed in 91 patients aged between 1 and 19 years with metastases of osteogenic sarcoma (40), nephroblastoma (24), Ewing sarcoma (12) and various other tumours (15).

Results: There were no perioperative deaths, and only one serious complication: chylothorax necessitating re-operation. Twenty-three patients are currently alive (26%), two with residual disease. Twelve patients (50%) with nephroblastoma aler alive; 7 patients with osteogenic sarcoma (18%) and 4 with other tumours (27%). Negative prognostic factors were: incomplete excision, primary tumour not controlled, or metastases developing during treatment. Not of significant influence on

the outcome were: the number of metastases developing during treatment. Not of significant influence on outcome were: the number of metastases, the disease free interval, unilateral versus bilateral metastases, pre-operative and postoperative adjuvant treatment of the number of thoracotomies performed.

Conclusion: The most important prognostic factor is the type of primary tumour. Excision of lung metastases in children with Ewing or soft tissue sarcoma is not warranted. All other patients who are able to withstand a major operation, should not be denied the chance because the surgical risks appear minimal and the outcome cannot be predicted beforehand.

331

METASTATIC AND LOCALLY RECURRENT HEPATOBLASTOMA (HB) PROBLEMS OF DIAGNOSIS AND THE ROLE OF SURGERY—RESULTS FROM THE SIOPEL I STUDY

J. Plaschkes

Department Pediatric Surgery, University Children's Hospital, Bern, Switzerland on behalf of the SIOPEL Core Committee, and YRCO Statistical Centre, Leeds, U.K.

In the SIOPEL I Study for Hepatoblastoma and Hepatocellular Carcinoma in children 155 cases of Hepatoblastoma (HB) and 40 cases of Hepatocellular Carcinoma (HCC) were accrued from Jan 1990–Febr 1994.

20% of children with hepatoblastoma and 28% of children with hepatocellular carcinoma presented with lung metastases. According to protocol all were treated by pre-operative chemotherapy with 6 courses of PLADO (Cis Platinum 80 mg^2/over 24 hours and Doxorubin 60 mg^2/over 48 hours) and delayed surgery of the primary tumour.

In **Hepatoblastoma** complete resection of the primary tumour was achieved in 60% of the patients and the overall survival is 68% (compared to 86% in non metastatic patients) at 18 months.

So far in this group 3 patients have had surgery for lung metastases and 2 for local recurrence. 2 of the 3 with lung surgery are alive with NED—1 died (cause at present not known).

1 has had surgery for local recurrence and is alive with slightly raised αFP. The other at present is lost to follow up. The data above will be updated and examined in more detail.

Patients with hepatocarcinoma are also being similarly evaluated.

332

SURGICAL TREATMENT OF RECURRENT AND METASTATIC DISEASE IN CHILDHOOD HEPATOBLASTOMA

D. von Schweinitz

Department for Pediatric Surgery, Medical School Hannover, 30625 Hannover, Germany

Malignant hepatoblastoma is the most common pediatric liver neoplasm occurring predominantly in children between 6 months and 3 years. Prognosis of these patients has been dismal but recently could be improved by the use of effective chemotherapy in multicentric cooperative trials. Yet, children with metastates or recurrent tumour usually have a poor outcome. Our experience is based on 103 children with hepatoblastoma operated on in our department 1977–1987 (group I: 30 pat.) or treated in the nationwide German pediatric liver tumour study HB89 1988–1993 (group II: 73 pat.) The disease-free survival was 37% (11/30) in group I and 74% (54/73) in group II. The patients' data show that primary complete resection of small tumours means an excellent prognosis (26/27 pat. disease-free). In contrast, 7/30 group I patients suffered from early local relapse or metastases after incomplete primary resections and 3/30 died under the operation. Therefore, large metastatic hepatoblastomas should be treated with chemotherapy prior to resection which reduces surgical complications, improves resection rates, and prevents early relapses. Primary chemotherapy containing doxorubicin, cisplatin, and ifosfamide was effective in reducing the tumour in 46/47 patients (98%) and 40 (85%) of them became resectable. Yet, 8/12 hepatoblastomas receiving prolonged chemotherapy developed drug resistance. Therefore, persistent or recurrent tumour require alternative drug regimens. Then, even these patients can be brought into remission after removal of all neoplastic tissue (6 patients in our series). Repeated surgery can be necessary to reach this goal. Lung metastases can be locally excised while recurrent tumour in the liver poses more problems, since it often occurs multifocally disseminated. Liver transplantation might cure these children (2/3 pat. in our series) but is only indicated, if there exists no extrahepatic tumour.

333

DNA SCREENING IN MEN FAMILIES AND THERAPEUTIC CONSEQUENCES

A. Frilling

Department of Surgery, University Clinic, 20246 Hamburg, Germany

Medullary thyroid carcinoma (MTC) may occur as a part of the inherited cancer syndrome multiple endocrine neoplasia type 2 (MEN 2). MTC is the only malignant and potentially lethal component of the MEN 2 syndrome. The underlying cause of MEN are missense mutations of the RET proto-oncogene located on chromosome 10q11.2. In MEN 2A the mutations affect one of the cystein residues in exon 10, 11 and 13. In these, the most common mutation is a Cys634 to Arg substitution. In MEN 2B families exclusively methionine mutations in codon 918 (exon 16) has been detected. Direct DNA testing for RET proto-oncogene mutations presents the method of first choice in presymptomatic screening in MEN 2 families. Gene carriers should be offered prophylactic thyroidectomy in the childhood. Non-gene carriers may be excluded from further screening.

334

NO ABSTRACT

335

IDENTIFICATION OF INDIVIDUALS WITH A GENETIC PREDISPOSITION FOR COLON CANCER—HNPCC

A. Lindblom

Department of Clinical Genetics, Karolinka Hospital, S-171 76 Stockholm, Sweden

Individuals from families with an inherited predisposition for colorectal cancer comprise a high risk population which would benefit from screening with colonoscopy and/or profylactic surgery. Hereditary non polyposis colon cancer is one of the most common genetic diseases in the Western world. As much as 1 in 200 can be a gene carrier and this syndrome is estimated to account for 5–10% of all colon cancers.

These families are identified by frequent cases affected with colon cancer, often early onset and right sided. The predisposition shows an autosomal dominant mode of inheritance. The predisposed individuals also have an increased risk for cancers in other sites such as uterus, stomach, ovary and breast. Individuals at 50% risk are offered screening with colonoscopy. In families with other frequent tumors available screening for these are offered as well. Gene carriers identified by mutation analysis in any of the genes known to cause disease in these families have almost 100% risk of developing cancer and are offered screening procedures or prophylactic surgery.

336

IDENTIFICATION OF CANCER PRONE INDIVIDUALS BY TAKING A FAMILY HISTORY—FROM MAN TO DNA AND BACK

W. Weber

Medical Oncologist, Swiss Cancer League, P.O. Box 8219, CH-3001 Bern, Switzerland

The Basel Familial Cancer Study Group concentrates on the family history for cancer control. Results of the first 1000 cancer patients interviewed:

29% have one, 10% two, 5% three or more first degree relatives with cancer. 9% have one or more first degree relatives with the same malignancy.

DNA is stored and analyzed from members of conspicuous families. Germlike mutations are identified in colorectal and breast cancer families. Persons affected are entered into preventive pilot studies (endoscopy, sulindac, tamoxifen, psychosocial evaluation). The family history is becoming an important element in national early detection efforts of the Swiss Cancer League.