local failure after breast conserving primary treatment. The purpose of this work is to report about the treatment results of 13 patients treated with local excision of the tumor recurrence followed by PDR-Brachytherapy.

Methods: From 1994 to 1996 thirteen patients with recurrent breast carcinoma after initial breast conserving therapy were treated with local tumor excision in association with postoperative PDR-Brachytherapy. Primary treatment consisted of lumpectomy or quadrantectomy followed by 50 Gy adjuvant external beam irradiation on the whole breast in eleven cases. A boost of 10 Gy was additionally given in seven of these patients. Another two received an HDR-Brachytherapy boost of 7 Gy and 8 Gy respectively. One female received 60 Gy on the whole breast and one was treated with 42 Gy orthovoltage therapy. Recurrences occurred mean 59 months (from 11–208 months) after primary treatment. In all cases PDR-Brachytherapy was given in a curative intention after a second try of breast conserving surgery. Treatment was performed under general anaesthesia using the classical plastic tube technique. For treatment planning orthogonal images in two planes were used. Dose calculation and prescription was performed according to the recommandations of the Paris system. Clinical target volume (CTV) was defined as the former tumorbed with a 2 cm safety margin. The peripheral dose entirely encompassed the CTV. Prescribed dose was 0.8 Gy per puls, total dose ranged from 16 to 50 Gy. In eight cases radiotherapy was performed by PDR-Brachytherapy alone. Five patients with got an additional EBT from 12 to 30 Gy.

Results: Eleven out of thirteen patients are locally free of disease with a median follow up of 19 month (range 5–38 month). In two cases another local recurrence after treatment occurred 4 and 8 month later and consequently those women were salvaged with mastectomy. Another two patients without evidence of local relapse failed distantly with bone metastases. Despite of the previously performed radiotherapy no severe side-effects are observed at present. Side effects are a moderate fibrosis grade 1–2.

Conclusion: Local tumor excision combined with PDR-Brachytherapy in case of small local failure after primary breast conserving therapy is a feasible and well tolerated method, which can prevent breast cancer patients from mastectomy. Although follow up time is short preliminary experience is encouraging.

712 PUBLICATION

A new active combination of tamoxifen (T)-vinorelbine (V)-anthraciclines in metastatic breast cancer (MBC)

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Purpose: Experimental data show that T acts through several cellular pathways which are not always Estrogen Receptor-dependent (Gelmann EP, 1996). Chadjaa (ASCO, 1993) and Spielmann (JCO, 1994) obtained significant results with a combination of anthaciclines (Adriamicin A – Epirubicin E) and Vinorelbine (V). We started the present study to assess the clinical benefit of the new following schedules: TAV: T 60 mg/die, d 1-2-3; A 25 mg/m^2 d 2; V 25 mg/m^2, d 2 every 2 weeks or TEV· the same doses of T and V plus E 50 mg/m^2, d 2, every 3 weeks.

Methods: From 2/93 to 10/96, 35 patients (21 TAV and 14 TEV), average age 58.8 (38–79), 10 pt over 65 years old, PS 0–2, are evaluable for response and toxicity assessment. Previous treatments included chemotherapy (65.7%), 13 pt as 2nd line, 6 pt as 3rd line and 4 pt as 4th line, hormones (28.5%) and radiotherapy (45.7%). Sites of metastatic disease were bone (63%), lung (46%), liver (40%), lymph nodes (28.5%), skin (20%), retina (5.7%). A total of 203 cycles was administered, average 5.8 cycles/pt, range 2–17. The patients were treated since achievement of CR, or since progression disease or since unacceptable toxicity.

Results: Because we included in this study also patients heavy pretreated, we considered in our results the overall objective tumor response inclusive of stable disease (total tumor growth control). Response rate was 85.7% (CR 8.5%, PR 45.7%, SD 31.4%). The median duration of CR was 12 months, of PR and SD was at least 3 months. 5 pts (14.3%) showed progressive disease during chemotherapy. WHO grade II and III leukopenia occurred in 10 pts (28.5%) and it was observed in 5 pts after 2° cycle and in 5 pts after 4° cycle; in 5 pts G-CSF was given. Cardiac impairment grade 2 was observed in 2 pts.

Conclusions: these results confirm the high activity of TAV-TEV combinations, the excellent tolerance profile, low morbidity. This interaction between T and V+anthraciclines should be particularly studied for first-line treatment in metastatic breast cancer to provide more impressive results.

713 PUBLICATION

Induction preoperative chemotherapy with high-dose epirubicin in locally advanced breast cancer (LABC)

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From January 1994 to June 1996, 47 patients (pts.) with LABC were treated with Epirubicin 150 mg/m2 i.v. every 15 days for 3 courses + G-CSF. Characteristics of the pts.· median age 47 years, performance status (ECOG) 0–1, T > 3 (median tumor size 7 cm), N1, M0.

Results in 47 evaluable pts.: 2 (4.2%) complete pathologic responses, 21 (44.7%) partial responses >50%, 4 (8.5%) partial responses <50%, 20 (42.6%) stable diseases; 6 (12.7%) pts. showed pathologic negative axillary nodes. After median follow-up of 10 months (range 6–30), 3 pts. had disease relapse and 6 pts died.

A longer follow-up to define the disease free survival and overall survival is needed.

714 PUBLICATION

Phase II trial of paclitaxel (P) and cisplatin (CDDP) in patients with advanced breast cancer refractory to anthracycline (A) therapy

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Introduction: The observation of clinical response induced by P among pts with A-resistant breast cancer were of particular interest after the demonstration of in vitro cross-resistance between P and other agents to which resistance is due to P-glycoprotein-mediated pleiotropic drug resistance.

Methods: From March until December 1996, 22 consecutive pts entered this phase II trial; all pts had received previous chemotherapy containing doxorubicin or Epirubicin, and all pts showed disease progression while receiving the A-containing regimen or after a response lasting less then six months. 12/22 pts had received two or more chemotherapic regimens for advanced disease. Metastatic sites included liver (10), lung (9), bone (13), lymphnodes and skin (4), liver was predominant site in 8/22 pts; multiple metastatic sites in 18/22 pts. P 135 mg/sqm was administered IV by a 3-hour infusion, followed by intravenous CDDP 75 mg/sqm, on day 1, every 3 weeks.

Results: At the present analysis 112 cycles of treatment have been given (range: 2–8; median: 5), and two pts are not yet evaluable for response. Among 20 pts evaluable (4 of whom are still receiving therapy), 7 (35%) have had a partial response, 11 (55%) achieved a stabilisation of metastases, and 2 progressive disease. Neuropathy and arthralgia/myalgia syndrome were the most frequently occurring toxicities. Treatment was delayed because of slow haematological recovery in 13/112 courses. Nausea-vomiting G2-G3 WHO in 25/112 courses, mucositis G3 in 11/112.

Conclusion: P-CDDP is a safe regimen in the treatment of pts with advanced breast cancer refractory to A therapy. In a patient population with a very poor prognosis it has showed moderate clinical activity and the rule of higher dosages of P should be investigated.

Colorectal cancer I

715 ORAL

Are disseminated tumor cells detected by RT-PCR in patients with colorectal cancer of prognostic value?

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Purpose: In a prospective study we evaluated the consequences of the detection of disseminated tumor cells on survival in patients with colorectal cancer.

Methods: We developed a cytokeratin 20 specific nested RT-PCR for the detection of disseminated tumor cells in bone marrow and venous blood. Samples of both compartments were aspirated prior to operation.

Results: Bone marrow from 79 patients and blood specimens from 53 patients were analysed. For the statistical analysis only patients with R0

resections and first operation due to colorectal cancer were included (n = 48 bone marrow, n = 39 blood, (28 sets of samples)). In 23% of these patients CK 20 cDNA was detected in bone marrow samples. The analysis indicated an increased detection rate correlating to the stage of disease (UICC classification). One positive result was detected in stage I (12.5%), 14.3% in stage II, 27.3% in stage III and 50% in stage IV. Survival of patients with positive findings in bone marrow was significantly shorter than in patients with a negative result for CK 20 ($p = 0.0011$). This could also be demonstrated for patients with equal tumor stages. Analysis of blood samples showed only 3 positive results (all corresponding bone marrow samples were also positive).

Conclusion: Cytokeratin 20 seems to be a marker for the detection of epithelial tumor cells in bone marrow. Our data demonstrate a correlation between the expression of CK 20 cDNA in bone marrow specimens and patients survival. The analysis in blood samples resulted in a lower detection rate.

716 ORAL

Evidence for different site-related genetic mechanisms in the pathogenesis of sporadic colorectal cancer

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Purpose: DNA tecnology is having an important role in the understanding of the pathogenetic mechanisms of colorectal cancer. The aim of the present study was to analyse some genetic alterations in sporadic colorectal carcinoma.

Methods: This study included 87 patients who underwent radical surgery for colorectal carcinoma. Allelic loss on chromosome 17p, mutation of p53 and k-ras, expression of c-myc were assessed for each tumor specimen and related to some clinicopathological variables.

Results: The frequency of deletion of 17p was higher in distal (90 9%) and rectal (71.9%) tumors than in the proximal ones (16.6%). Mutation of p53 was found to be more frequent in distal (76.0%) and rectal (64.7%) tumors than in the proximal ones (33.3%). Overexpression of c-myc was more frequent in distal (88.0%) and rectal (73.5%) tumors than in the proximal lesions (53.5%). Mutation of k-ras tended to be more frequent in rectal tumors (58.8%) than in the distal (32.0%) and proximal (39.2) ones.

Conclusions: The present study suggests that inactivation of tumor-suppressor genes and activation of oncogenes are involved in the carcinogenesis of distal and rectal tumors in sporadic colorectal cancer; on the contrary, the majority of proximal colon tumors seems to develop through different genetic changes.

717 ORAL

Influence of low dose sulindac on p53 proteins, on BCL-2 protein and on TGFα in rectal mucosa biopsies of cancer prone patients (FAP) in a chemopreventive trial

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Purpose: Influence on p53 proteins (wt/mut), on the apoptosis blocker *bcl*-2, and on tumour growth factor alpha (TGFα) are investigated to explain the antiproliferative effects of sulindac in a chemopreventive NSAID-trial on rectal adenomas and mucosa of familial adenomatous polyposis patients (FAP).

Methods: Ongoing, prospective, controlled, non-randomised phase II-dose finding study. Rectal sulindac application after colectomy and ileo-rectal anastomoses (study group:n = 28, control group:n = 10).18 months of immunohistochemical follow-up evaluable. Proliferation markers (MIB1, PCNA), p53, *bcl*-2, and TGFα stained on frozen/paraffin sections. p53 quantified using ELISA-kits.

Results: Obvious reduction in polyp counts, 78% complete adenoma reversions at last reexamination at 64 mg sulindac as mean daily dosis/person. Mucosal proliferation stabilization correlates to reduction of p53 proteins in untreated vs. treated mucosa (ANOVA, $p < 0.05$). *bcl*-2/p53 overexpression inversly correlates in adeno-matous mucosa of controls and microadenoma relaps. Insignificant changes of TGFα to reduction of sulindac doses.

Conclusions: Low-dose rectal sulindac is highly effective in maintaining adenoma reversion. p53 protein reduction and supposed induction of apoptosis via *bcl*-2-upregulation possibly stabilize mucosal proliferation. TGFα-expression as a proliferating stimulous of adenomatous tissue showed no dose related change.

718 ORAL

Clinical impact of immunoscintigraphy with ^{99m}Tc-labeled anti-cea Fab' in the follow-up of colorectal cancer patients: Prediction of surgical resectability from the combination with CT

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Purpose: Conventional radiological methods (e.g., CT) have only limited diagnostic accuracy. The aim of this study was to evaluate immunoscintigraphy with ^{99m}Tc-labeled anti-CEA Fab' (CEA-Scan®) alone and combined with CT in the follow-up of colorectal cancer patients.

Methods: At our department, 22 colorectal cancer patients were examined with CEA-Scan® (Immunomedics, Morris Plains, NJ, USA) during their postsurgical follow-up, using whole-body single photon emission computed tomography. All results were compared to those of CT. Final evaluation was performed in relation to postsurgical histology. The potential impact of immunoscintigraphy on the surgical management was analyzed with respect to a correct preoperative judgement of the patients' resectability. These data were compared to those of a multicenter trial involving 272 colorectal cancer patients (88 of them with occult disease).

Results: The lesion-based sensitivity of immunoscintigraphy was 94%, the diagnostic accuracy 92%. The sensitivity was independent of CEA serum levels. Less than 1% of patients developed HAMA. In the occult-disease group of the multicenter trial, the diagnostic accuracy was 93%. If CEA-Scan® and CT were concordant with respect to resectability, this judgement was correct in all cases, whereas in 88% of the discordant cases, the immunoscintigraphic result was correct. The combination of CEA-Scan® and CT improved the diagnostic accuracy from 83 to 93% ($p = 0.0005$).

Conclusion: These results show that CEA-Scan® is able to detect and localize recurrent colorectal cancer accurately. The use of antibody fragments avoids HAMA formation. The combination of immunoscintigraphy and conventional imaging procedures allows for an improved non-invasive estimation of surgical resectability.

719 ORAL

Accuracy of laparoscopic colorectal resection for cancer: A prospective multicenter study

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Laparoscopic colorectal surgery for cancer is presently under discussion. A prospective observational multicentre study was initiated on Aug. 1, 1995, in the German-speaking countries of Europe. We present the results after one year with respect to the accuracy and quality of oncological resections. Out of 500 operations, 231 (46%) were performed for cancer, 167 (33%) with curative intent. The mean age of the patients was 66 years (CI 5–95%: 64–68) and the male-to-female ratio was 1 0. The most common curative resections were: 63 anterior rectum resections (38%), 51 sigmoid resections (30%), and 27 amputations of the rectum (16%). Segmental resections were performed in 20 patients (11%) in selected indications. Intraoperative tumour spillage was reported in 2% Resection margins were tumour-free in every case. The mean number of lymph nodes harvested was 13.0 (CI 5–95%: 11.5 to 14.6), with significant differences between participating (Kruskal-Wallis, DF = 12, $p < 0.0001$). In the case of anterior resections, the mean distal resection margin was 39 mm (CI 5–95%: 33 to 45). Comparison of these results with recent data obtained by the German Study Group Colo-Rectal Carcinoma (SGCRC) for conventional colorectal surgery revealed no relevant differences between laparoscopic and open colorectal surgery in terms of the oncological quality criteria. The surgeon appears to be a risk factor in both surgical modalities. Since the incidence of port-site metastases and long-term survival after curative laparoscopic surgery for colorectal cancer are still unknown, we continue to recommend that such operations should not be performed outside the confines of a prospective study.