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Effect of Cytokine Secretion Capacity at Diagnosis on Survival in Non-Small Cell Lung Cancer (NSCLC)

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Background: Increased production of immunosuppressive interleukin-10 (IL-10) by NSCLC and increased plasma IL-10 concentrations in NSCLC patients have recently been correlated to reduced survival. We earlier demonstrated suppression of IL-2 secretion in whole blood cell cultures of NSCLC patients. We now analyzed the influence of IL-2 secretion on survival in NSCLC patients and the influence of IL-10 on IL-2 secretion.

Methods: IL-2 secretion in whole blood cell cultures was measured by ELISA prior to therapy in 90 NSCLC patients. The correlation of IL-2 concentration at the time of diagnosis to survival was calculated by *crit-level*, the Kaplan-Meier method, and the log-rank-test. For multivariate analysis of prognostic factors the Cox model was used.

Results: With a cut-off value of 1,100 pg/ml IL-2 the difference in survival was significant with a *p* value of 0.014. In the group with high IL-2 (*n* = 38, 29 failures) and low IL-2 (*n* = 52, 47 failures) median survival was 14.1 and 9.7 months, respectively. In the subgroup of 33 surgically treated patients the difference in survival was significant with a *p* value of 0.011. In 14 patients with surgical resection of the tumor and high IL-2 at diagnosis and 19 patients with surgical resection but low IL-2 at diagnosis, median survival was 86.2 and 11.3 months, respectively. By multivariate analysis, metastasis, CEA and IL-2 secretion capacity were independent prognostic factors with *p* values of 0.001, 0.03 and 0.024, respectively. Secretion of IL-2 in whole blood cell cultures from healthy individuals was inhibited in a dose-dependent way upon addition of IL-10.

Conclusions: IL-2 secretion capacity was correlated to survival in NSCLC patients and had major prognostic relevance. Suppression of IL-2 secretion by immunocompetent peripheral cells could be inhibited

in a dose-dependent way by IL-10. Since tumor-mediated increase of IL-10 has been connected to reduced survival in NSCLC, decrease of IL-2 secretion associated with reduced survival could therefore well be mediated by tumor-derived IL-10.

Tumor Invasion or Tumor Impression? – Endobronchial Ultrasound (EBUS) Allows Differentiation in Patients with Lung Cancer

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Purpose: Invasion of the tracheobronchial wall by tumor affects strategies of surgical therapy. The current gold standard for diagnosis is cat scan of moderate accuracy. Therefore, we investigated EBUS as it proved accurate in high-resolution imaging of the tracheobronchial wall.

Method: In a prospective study patients with central tumors who were considered to be candidates for surgery, underwent additional examination by endoscopic ultrasound during regular staging. The results were compared to the intraoperative and postoperative pathological findings.

Results: In 131 patients with central tumors, EBUS and CT findings were classified by independent examiners. 105 patients (27 f, 78 m, mean age 59.2 years) underwent surgery and could be evaluated. By EBUS tumor invasion was diagnosed in 49 and tumor impression in 56 cases, by CT invasion was detected in 81 and impression in 24 cases. Intraoperatively 55 patients showed tumor invasion and 50 impression. The accuracy of EBUS was 94%, the sensitivity 89%, and the specificity 100%. For CT the accuracy was 51%, the sensitivity 25%, and the specificity 80%. No adverse effects were observed.

Summary: EBUS allows differentiation of tumor invasion from impression with much higher accuracy than cat scan. Thus, in staging of patients with central tumor growth EBUS could gain an important role in the future.

Nonmyeloablative Stem Cell Transplantation in Multiple Myeloma

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Background: Existence of a graft vs. myeloma effect has been well documented by responses to DLI and long-term survival after allogeneic bone marrow transplantation. But the more widespread use of allogeneic transplantation in multiple myeloma (MM) has been limited by the high rates of nonrelapse mortality in these older and heavily pretreated patient group. We hypothesized that a lymphoablative conditioning which is nonmyeloablative can be used to allow engraftment of allogeneic cells without excessive regimen toxicity or GVHD in MM patients.

Patients and Methods: From August 1999 to October 2000, 12 patients with MM have received related ($n = 5$) or unrelated ($n = 7$) allogeneic bone marrow ($n = 1$) or blood stem cell transplantations ($n = 11$). For conditioning 2 patients received 2 Gy TBI alone, in the other patients fludarabine was combined with TBI ($n = 9$) or melphalan 140 mg/m² ($n = 1$). Posttransplant immunosuppression consisted of cyclosporine and mofetil mycophenolat. Two patients received T-cell depleted grafts, and 10 patients received unmanipulated grafts with a mean cell number of 5.8×10^6 CD34⁺ cells/kg. Mean age of patients was 48 years. Median time from diagnosis to transplant was 56 months, and all patients were heavily pretreated, with all but one patient having had at least one previous high-dose chemotherapy with autologous stem cell support. At the time of transplant 2 patients were in CR, 4 had stable disease, and 6 had progressive disease despite conventional therapy.

Results: Treatment was well tolerated with no transplant-related deaths. All patients engrafted, with 5 patients never dropping neutrophil counts below $0.5 \times 10^9/l$. All but 1 evaluable patients had mixed chimerism >50% by day 50 and >75% by day 100, with the majority achieving >95% donor chimerism documented by molecular techniques. 2/12 patients developed acute GVHD grade II, which responded well to steroid therapy, no grade III–IV acute GVHD developed. With a median follow-up of 128 days 10 patients are alive while 2 patients died due to progressive disease. Five patients are either in PR ($n = 2$) or CR ($n = 3$), and 7 patients progressed, with 2 patients showing malignant cells in cerebrospinal fluid collections without evidence for systemic disease progression.

Conclusion: Allogeneic transplantation after nonmyeloablative conditioning can be safely performed in heavily pretreated patients with MM, even with an unrelated donor. Transplant-related mortality and morbidity is very low; for interpretation of response and survival longer follow-up is needed.

Intrathecal Treatment of Relapsed Mantle Cell Lymphoma with Rituximab in Combination with Standard Chemotherapy. A Case Report

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Background: In malignant lymphoma, primary central nervous system (CNS) involvement is rare. Later on in disease about 10% of patients show CNS relapse, in mantle cell lymphoma only 4% show CNS involvement. However, the clinical course and prognosis in patients with CNS relapse is poor. Most of CNS lymphomas are B-cell neoplasms, with expression of CD20 surface antigen. Rituximab, a

human chimeric anti-CD20 antibody has shown response in cases of CNS lymphoma. However, only 1–1.7% of the corresponding serum concentration levels could be reached in cerebrospinal fluid (CSF) when Rituximab was given as intravenous infusion. Therefore, intrathecal application of Rituximab with higher anti-CD20 concentration in CSF is promising.

Methods/Case: We report on a 68-year-old man with mantle cell lymphoma, first diagnosed 1998. Since 1998 he received various chemotherapy regimes consisting of fludarabine, mitoxantrone, dexamethasone, bendamustine and Rituximab (intravenous application). In 3/2001, 7 months after the last application of Rituximab, CNS relapse was diagnosed with intracerebral and meningeal manifestation. After intrathecal therapy with MTX and irradiation of CNS he showed a complete remission. In 8/2001 the patient reported on pain in his arms and shoulders, again a CNS relapse with meningeal lymphomatosa was diagnosed in CSF, no other manifestations could be found. We decided to treat the patient with intrathecal Rituximab. From 8/2001 until 9/2001 the patient received 8 intrathecal applications of Rituximab 25 mg in 2.5 ml 0.9% saline, and MTX 15 mg, ARA-C 40 mg as well as dexamethasone 4 mg.

Results: The intrathecal application of Rituximab in combination with standard chemotherapy was well tolerated. No toxicity or clinical side effects were observed. The patient reached a complete ongoing remission.

Conclusion: The intrathecal application of Rituximab is well tolerated and seems to be a therapeutic option for CD20-positive lymphomas with CNS involvement. Further studies with more patients are necessary.

Real-Time Quantitative PCR for the Surveillance of Chronic Myeloid Leukemia Patients after Allogeneic Stem Cell Transplantation

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Background: Patients with chronic myeloid leukemia (CML) after allogeneic stem cell transplantation should be monitored in a sensitive, meaningful and easy-to-perform way to detect potential relapse early when intervention is most successful.

Methods: Here we developed a real-time quantitative RT-PCR (RQ-PCR) assay based on TaqMan technology to quantify the *bcr-abl* translocation found in CML. 33 patients with CML in first chronic phase ($n = 23$) or advanced disease ($n = 10$) received allogeneic bone marrow ($n = 27$) or peripheral blood stem cell ($n = 6$) transplantation from related ($n = 12$) or unrelated ($n = 21$) donors after conditioning therapy with a high-dose busulfan-based regimen ($n = 27$) or a low-intensity protocol comprising fludarabine, BCNU and melphalan ($n = 6$). A total of 541 peripheral blood and bone marrow samples taken at various time points after transplantation were investigated by RQ-PCR.

Results: The RQ-PCR assay detected up to 1 CML cell in a background of 10^5 normal cells. Correction for the varying RNA quality by normalization with the housekeeping gene *GAPDH* (*bcr-abl*/*GAPDH* ratio) proved mandatory for meaningful quantitative results. 12 of the 33 patients were treated for relapse (e.g. by donor lymphocyte infusion (DLI) or IFN- α), and in these cases RQ-PCR showed increases of *bcr-abl*/*GAPDH* over time, which preceded hematologic relapse up to 630 days. Response to treatment could be monitored by decreasing *bcr-abl*/*GAPDH* ratios.

Conclusions: RQ-PCR of *bcr-abl* should be the preferred method for the surveillance of CML patients after allogeneic transplantation. As

a sensitive PCR-based assay it may lead to detection of presumptive relapse early when intervention is most successful. It allows decisions based on the amount of *bcr-abl* transcripts and in particular on their dynamics (increase, decrease) as opposed to mere qualitative RT-PCR which might not be informative. The RQ-PCR assay is a robust, reproducible and easy-to-perform technique with built-in control for RNA quality, suitable for routine clinical use.

Allogeneic Hematopoietic Cell Transplantation from Unrelated and Related Donors in Patients with Active Disease $\geq$ 60 Years of Age

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The widely accepted upper age limit for related or unrelated donor transplantation is 60 or 55 years. Here we present our results of 23 patients with a median age of 63.6 (range 60–70.5) years, transplanted from a matched sibling ($n = 9$) or unrelated ($n = 14$) donor. Patients diagnosis were AML/MDS, MDS RA, CMML, NHL and CLL. Except for 1 patient each in CR1/2 or CP2, all patients had active disease with primary refractory or untreated AML/MDS ($n = 18$), relapsing or advanced NHL/CLL. For conditioning a regimen (FBM) with fludarabine $5 \times 30 \text{ mg/m}^2$, BCNU $2 \times 150 \text{ mg/m}^2$ and melphalan 110 mg/m^2 was used. GvHD prophylaxis consisted of CSA, and Mtx or MMF, and in unrelated transplants patients received ATG-S® (Fresenius) 40–60 mg/kg additionally. 1 patient died from mucor day +28 prior to engraftment, all other patients engrafted with leukocytes $\geq 1.0 \times 10^9/\text{l}$ day +11 and platelets $> 20 \times 10^9/\text{l}$ day +14 in median. Rates of acute GvHD II–IV were 55% (75% in related and 35% in MUD transplants). TRM was 21% in the majority due to fungal infection in this heavily pretreated and advanced disease population. 21/23 patients (91%) achieved CR, and 2 patients died before disease evaluation. 4/21 patients relapsed, 2/4 achieving again CR after donor lymphocyte infusion (1) or second transplantation (1). OS and PFS is 65% and 56%, respectively, with a median follow-up of 16 (6–23) months.

Conclusion: Age as such should not be used as exclusion criteria for allogeneic transplantation. Transplantations with a MUD are safe and effective. TRM is determined by disease state and pre-treatment. FBM regimen has high activity in active myeloid and lymphoid malignancies.

Specific Inhibition of Tumor Angiogenesis vs. Metronomic Chemotherapy

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Background: Chemotherapy is effecting tumor cells as well as endothelial cells. The application of low-dose continuous (metronomic) chemotherapy may optimize the effect on the tumor endothelial cells, acting like an unspecific antiangiogenic regimen. Therefore, we evaluated clinically relevant cytotoxic agents for their IC-50 on endothelial cells as well as on different tumor cell lines. Additionally, the most promising compounds were studied in metronomic doses in a murine renal cell carcinoma model and compared with specific angiogenesis inhibition (VEGF-receptor inhibitor) to investigate their antitumor and antiangiogenic activity in vivo.

Methods: For in vitro studies, influence of different cytotoxic agents on proliferation (BRdU assay) and apoptosis (FACS analysis) were studied on tumor cell lines as well as on endothelial cell lines to determine IC-50 and mechanism of action. For in vivo studies, intrarenal application of RENCA cells in syngenic Balb/c mice was used. 21 days after application, mice developed a primary tumor and metastases to the lung and abdominal lymph nodes. Mice received either 12 mg adriamycin i.v. on day 10 and 17 or 1,2 mg adriamycin i.v. on day 10 and 17 or 0,24 mg adriamycin i.v. on day 10–19, 50 mg of specific VEGF-receptor inhibitor or vehicle. All mice were sacrificed on day 21 and tumor weight and volume, lung weight and lung metastases as well as vessel density in primary tumors (immunohistochemical staining against CD-31) were detected.

Results: The IC-50 of cytotoxic drugs (adriamycin, idarubicin, 5-FU, paclitaxel) is decreased by 3 orders of magnitude or more for the endothelial cells compared to different tumor cell lines. Adriamycin, applied at cyclic MTD to RENCA mice, resulted in a partial remission in tumor volume but showed increased vessel density in primary tumors compared to the control group. Metronomic application of adriamycin resulted in a partial remission of tumor volume but showed a significant decrease in vessel density of primary tumors as by the use of VEGF-receptor inhibitor.

Conclusions: The application of cytotoxic drugs in the metronomic way shows clear antiangiogenic efficacy that is comparable to specific inhibition of angiogenesis. It therefore may become a future alternative to conventional applied chemotherapy.

Treatment of a Patient with a Granulosa/Theca Cell Tumor of the Ovary with STI571 (Gleevec)

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Introduction: Fewer than 10% of all ovarian tumors are of stromal origin. The granulosa cell tumor is composed of granulosa cells with or without an admixture of theca cells. This tumor can be associated with hyperestrogenism resulting from tumor-related estrogen secretion. These tumors tend to have a more indolent course. However, once granulosa cell tumors have disseminated, there is no standard treatment; radiotherapy and chemotherapy are of little benefit.

Case Report: We report on a 87-year-old woman who presented to another hospital with abdominal pain (01/2000). There was a palpable mass in her abdomen and a CT scan showed a tumor of the left ovary with suspected peritoneal spread. A laparotomy was performed, and the tumor with the left adnexes and an infiltrated part of the small bowel were resected. Histologic workup revealed a granulosa/theca cell tumor infiltrating the small bowel wall. The patient received no additional treatment. 10 months later a sonographic examination of the abdomen showed multiple metastases in the liver. First the patient received a hormonal therapy (letrozole), thereafter a chemotherapy with idarubicin. Both therapies were ineffective, and in April this year we started a treatment with STI571 (Gleevec 100–200 mg per day). The patient improved significantly. The lesions within the liver melted down, the LDH level decreased from 603 to 397 U/l, and the liver enzymes markedly improved.

Conclusion: To our knowledge this is the first case in literature of a granulosa cell tumor responding to treatment with the novel tyrosin kinase inhibitor STI571. Immunhistologic examination of the tumor tissue concerning the expression of c-kit is underway and will be presented at the meeting.

Mastectomy + High-Voltage Irradiation +/- Systemic Therapies by 458 Consecutively Treated Female Breast Cancer (pT1/pT2)

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Objective: Analysis of the daily routine work (1979–1995) based on prospectively collected records and checks in regular intervals in our institution.

Material and Methods: (Compare title). Chest wall ≥ 60 Gy, lymph nodes 46–49 Gy. Radiotherapy stopped 4 cases, lost of control 9 cases. Follow-up median 180 (62–261) months. Age median 59 (25–91) years. Systemic therapies were registered against yes/no principle. We did neither influence nor carry out its realization.

Results (%): See table 1 (p. 4 bottom).

Conclusions: With the exception of LRFS – local therapy efficiency proved – all differences are statistical significant. In the systemic group the high-risk factors were clearly elevated. Their consequences will be discussed.

Breast-Conservation Treatment for Ductal Carcinoma in situ (DCIS) of the Breast

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Background: This study was performed to determine the long-term outcome for women with DCIS of the breast treated with breast-conserving surgery followed by definitive breast irradiation.

Methods: 64 women with a median age of 48.9 years with intraductal carcinoma of the breast were treated with breast-conserving surgery followed by radiotherapy of 45–50 Gy to the whole breast and a boost of 10–20 Gy to the primary site. Median follow-up was 8.7 years.

Results: 10 patients (15.6%) developed local failure at a median interval of 7 years after surgery. The local recurrence was invasive carcinoma in 7 patients. Treatment consisted of mastectomy in all cases. None of the patients developed distant metastases or died of breast cancer.

Conclusion: Local recurrences can be salvaged with excellent survival rates – supporting the idea of breast-conserving surgery and radiation as initial treatment of DCIS of the breast.

Toxic Encephalopathy in a Patient with Metastatic Breast Cancer and Capecitabine Therapy

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Central nervous toxicity is a rarely seen side effect of capecitabine therapy. We describe a 61-year-old female patient with extensively pretreated metastatic breast cancer and toxic encephalopathy under capecitabine treatment.

Breast cancer was first diagnosed in 1984 (initial stage pT3 pN1 M0 G2; ER and PR pos.). Primary treatment was quadrantectomy and radiotherapy. Metastases of the skin, bones and ipsilateral axillary lymph nodes were detected in 1987. The following therapies included hormone therapy with tamoxifen, megestrolacetate and letrozole, and chemotherapy with 3 courses docetaxel, doxorubicine and cyclophosphamide. While each hormone treatment induced a partial remission of several months, first-line chemotherapy resulted in stable disease only. Between January and April 2000 she was given capecitabine (4000 mg/day) and achieved a PR. No side effects were seen, except grade 2 diarrhea and grade 1 hand-foot syndrome during the last cycle. The patient remained progression-free for 14 months. In June 2001 disease progression was documented and capecitabine therapy was restarted on June 11. On June 15 the patient was admitted to the hospital for atrial fibrillation (AF). The medication on admission consisted of hydrocortisone for preexisting adrenal insufficiency and L-thyroxin for preexisting hypothyreodism. Both drugs had been given for >12 months without any side effects. The only new drug, given on admission, was metoprolol for the AF. On June 17 she was found with painful contractions of the throat and submandibular muscles, which led to dys- and anarthria and lasted for several hours. During this period the patient was fully conscious and remembered details of what happened around her. These episodes recurred 5 times in the following 2 days. A MRI revealed diffuse subcortical medullar alterations in both hemispheres and in the basal ganglia, without enhancement, which were interpreted as toxic changes. EEG was normal, even during the fits. Neurological examinations in the periods between the fits were normal. Therapy with oxcarbazepine was initiated and capecitabine was stopped. Since June 20 no more fits occurred. On August 21 a MRI showed complete regression of the pathologic findings, and antiepileptic therapy was reduced stepwise. The last dose was given on August 21.

Interpretation: This is the first report on a patient with toxic encephalopathy under treatment with capecitabine. It has to be assumed that the symptoms correspond to a central epilepsy. EEG remained normal, perhaps due to the fact that the CNS pathology was very central. Central nervous toxicity may thus be a rare but important side effect of capecitabine treatment.

Table 1.

Therapy	n	LRFS			DMFS			DFS			CSS			OS		
		5y	10y	15y	5y	10y	15y	5y	10y	15y	5y	10y	15y	5y	10y	15y
RT (pN+: 36.7%)	259	97	96	95	74	69	66	73	68	63	82	75	69	76	62	47
RT+syst. Th (pN+: 78%)	186	93	93	93	67	54	53	66	53	52	73	60	53	68	49	40
p-value		0.1			0.01			0.01			0.002			0.02		

Second-Line Treatment of Advanced Colorectal Cancer with Irinotecan, 24-Hour High-Dose 5-Fluorouracil (HD-5-FU) and Folinic Acid (FA) after Failure for HD-5-FU/FA

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Background: Irinotecan (IRI) has shown to prolong survival and improve quality of life compared to best supportive care in colorectal cancer (CRC) patients with pretreatment of bolus 5-FU. After first-line 24-hour HD-5-FU/FA an objective response rate of 12% with 3-weekly IRI 350 mg/m² has been reported [Schöffski, ASCO 2000;1155]. Toxicity (NCI-CTC 3–4) in this study was: neutropenia 16%; diarrhea 23%, nausea 12%. The present study investigated weekly IRI in combination with 24-hour HD-5-FU and FA as a second-line treatment after prior exposure to 24-hour HD-5-FU 2,600 mg/m² and FA 500 mg/m². Clinically known synergy between 5-FU and IRI was the rationale to combine both drugs for second-line therapy in order to overcome resistance to 5-FU. Weekly IRI was chosen to reduce toxicity compared to a 3-weekly schedule.

Methods: Patients (pts) were recruited in a single institution to receive 6× weekly IRI 80 mg/m², FA 200 mg/m² and 24-hour HD-5-FU 2,000 mg/m². Treatment was repeated on day 57.

Results: 35 pts (m/f 22/13; median WHO status 1; median age 61 (range 27–78) years) are evaluable for toxicity and 34 for response. Six patients (17%) achieved a partial remission. In 14 patients (40%) no change was observed, while in 14 patients (40%) disease progressed. Median time to progression was 112 days (4 pts censored) and overall survival was 263 days (19 pts censored). 80 treatment cycles are evaluable for toxicity (NCI CTC grade 3): leukopenia 4%, vomitus 3%, diarrhea 11.4%. No grade 4 toxicity was observed.

Conclusion: Weekly IRI/HD-5-FU/FA is an active combination chemotherapy with tumor control rates in the range of other IRI-based second-line schedules. The toxicity profile in our study appears to be favorable compared to 3-weekly IRI.

Multimodal Therapy of Squamous Cell Carcinoma (SCC) of the Esophagus

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Background: SCC of the esophagus is known as a tumor with poor prognosis in locally advanced or distant metastatic state. Perioperative radiotherapy or chemotherapy alone have no significant impact on survival, whereas neoadjuvant or definitive radiochemotherapy appears to be more promising.

Methods: We analyzed the data of patients with locally advanced (uT3/4, Nx) SCC of the esophagus who underwent surgical resection after neoadjuvant radiochemotherapy between 1996 and 2001. Preoperative staging included CT scan, endoscopic ultrasound and barium swallow. All patients received radiation to 40 Gy with 2 up to 4 cycles of fluorouracil (1,000 mg/sqm over 24 h days 1–5, rep. day 29) bi-modulated with folinic acid, and cisplatin (20 mg/sqm days 1–5, rep. day 29). After a 4- to 6-week interval surgical resection was carried out.

Results: 41 patients met the inclusion criteria during the 5-year interval. Of these, 16 (male, median age 62 years) were resected after neoadjuvant treatment. Dose reduction was necessary in 1 of these 16 patients, major toxicity (CTC grade 3–4) was seen in 2 patients: leukopenia grade 4 n = 1 and mucositis grade 3 n = 1. Operative morbidity was 44% including anastomotic leakage in 3 patients (19%). Two of 16 patients (12%) died, 5 and 13 weeks postoperatively due to complications of anastomotic leakage (pneumonia, mediastinitis). Unfortunately, complete histopathologic response (pCR) had been noted in these 2 patients. In 8 of 16 patients (50%) pCR could be achieved. The survival rate at 1 year was 69%. Only 1 patient with pCR has relapsed so far, whereas 6 of 8 patients without pCR have died of metastases.

Conclusions: Neoadjuvant radiochemotherapy is feasible with respect to toxicity. Perioperative morbidity and mortality in our series is comparable with other trials. The outcome of patients with pCR appears to be better than that of patients with residual tumor in the resected specimens.

Inoperable Esophageal Carcinoma: Functional Results and Macro- and Microscopical Elimination after Radiotherapy ± Chemotherapy

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Background: Whereas survival benefits are reported after combined chemoradiotherapy of inoperable esophageal cancer, functional results and elimination rates remain undetermined. Re-endoscopy during and after treatment should give information about local disappearance and can be compared with relief of dysphagia.

Methods: 135 patients are analyzed specifically considering macro- and microscopical elimination evaluated by re-endoscopy compared with swallowing abilities. A prospectively defined five-point score of swallowing was used. Two radiochemotherapy schemes were used: 5FU/cisplatin and low-dose carboplatin.

Results: 256 re-endoscopies were performed. 25 out of 135 patients received radiochemotherapy (13 5FU/cisplatin and 12 carboplatin) and showed a better elimination rate (54 and 58%, respectively, vs. 44%), no intransit tumors (0 vs. 4%) and a tendency of improved survival. No reduction of distant metastasis or local recurrence was noted. After radiochemotherapy with 5FU/cisplatin relief of dysphagia was considerably lower and recovering prolonged. Overall 86% could eat normally after treatment. 74 (55%) out of 135 patients had local persistency, local recurrence or intransit metastasis, but only 34 (25%) suffered again from dysphagia. Macro- and microscopical elimination lead to a doubled survival (median 13 months vs. 5.5–7 months).

Conclusions: Radiochemotherapy with carboplatin improved local elimination. In contrast relief of dysphagia with 5FU/cisplatin was considerably lower, mainly due to prolonged esophagitis. Incidence of local recurrence or distant metastasis was not reduced. Main effect of concomitant chemotherapy seems to be radiosensibilization and increase of local disappearance. Re-endoscopy to monitor response under/after therapy seems feasible, and results correlate significantly with survival. Relief of dysphagia was encouraging despite poor prognosis.

Simple Chemotherapy for Locally Advanced or Metastatic Gastric Cancer (LAMGC)

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Background: Locally advanced or metastatic gastric cancer has a poor prognosis. Thus, it is difficult to propose a chemotherapy to patients with a good performance status, even to those with linitis plastica.

Methods: We have retrospectively studied over a period of 10 years, between 1991 and 2001, those patients treated for an LAMGC using our actual standard protocol consisting of weekly high-dose 5-fluorouracil/folinic acid (FA 400 mg/m², 5-FU 2,400 mg/m² J1 = J8) at home, in first or second line.

Results: 18 patients (6 females, 12 males, median age 67 years) received this regimen: 61% of the treatments were first line and 39% were second or third line after platinum. 80% of these 18 patients (56% locally advanced disease and 44% metastatic disease) received gastrectomies, unusual in the palliative setting. Histologically, 12 patients (67%) had adenocarcinomas and 6 (33%) linitis plastica. 11 patients (61%) presented a clinical response after 3 months of treatment and 4 (22%) after 6 months. The median progression-free interval was 6.5 months. Six patients (33%) received further chemotherapy after progression on high-dose 5-FU/FA. The median survival time was 16 months with 2 patients alive after 24 months. Of the 6 patients with linitis plastica, the median survival time for this group was 17 months. None of the 18 patients experienced a toxicity higher than grade II: Diarrhea, stomatitis, and hand and foot syndrome were the most frequently observed toxicities.

Conclusion: Weekly high-dose 5-FU/FA is a simple treatment without severe toxicity and may be easily administered at home. This scheme offers patients with a highly unfavorable prognosis a satisfactory quality of life, even in second- or third-line therapy.

SMAD7 is a Prognostic Marker in Patients with Colorectal Cancer

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Deletion of chromosomal region 18q21 is frequently observed in colorectal cancer (CRC) and is associated with poor prognosis. This region includes genes encoding the TGFβ signaling mediators SMAD2, SMAD4 and SMAD7, and the adhesion molecule DCC. In order to evaluate the clinical relevance of the deletion of each of these genes, we took advantage of 325 archived biopsies available from a randomized study on benefit of adjuvant chemotherapy in patients with CRC. Gene copy dosage revealed that SMAD7 had a lower deletion frequency (43%) than SMAD4, SMAD2, or DCC (67%, 64%, and 54%, respectively). Multivariate analysis of these genetic data showed a favorable outcome for SMAD7 deletion [overall survival (OS): hazard ratio (HR) = 0.43, p = 0.001; disease free survival (DFS): HR = 0.50, p = 0.003]. In contrast, SMAD7 duplication had a hazardous effect on patient survival [OS: HR = 1.97, p = 0.049; DFS: HR = 1.99, p = 0.047]. Since SMAD7 blocks TGFβ signaling, these data are consistent with the hypothesis that loss of SMAD7 renders carcinoma cells more sensitive to apoptosis induction through the TGFβ pathway, whereas gain of SMAD7 function might result in

TGFβ resistance. No significant association was observed between deletion of SMAD2, SMAD4 or DCC and patient outcome. This suggests that the previously described poor prognosis associated with loss of the 18q21 region is not related to any of these genes. Interestingly, patients with SMAD4 deletion had less benefit from 5-FU-based perioperative chemotherapy than patients with normal SMAD4 copy number [OS: HR=3.23, p=0.06; DFS: HR=2.89, p=0.05], suggesting that 5-FU may act through components of the TGFβ pathway. In conclusion, loss of response to the apoptotic function of TGFβ is a key factor in cancer progression and might be clinically useful as prognostic and notably predictive marker in the treatment of colorectal carcinomas.

Docetaxel (DOC) and Irinotecan (IRI) Combination in Advanced Pancreatic Cancer (APC). A Phase II Study

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We report a phase II study of DOC combined with IRI in APC. Treatment schedule was DOC: 60 mg/m² i.v. 60 min day 1 and IRI: 250 mg/m² i.v. 90 min day 1 q3 weeks in an outpatient setting. Hematopoietic growth factors were given in case of febrile neutropenia or grade 4 neutropenia in the previous cycle. The study endpoints were: response rate, progression-free survival (PFS) and tolerance. 23 patients with non-pretreated APC were enrolled (median age 57 (43–67) years). The median number of cycles was 4 (1–14). 17 patients were evaluable for response (16 patients metastatic and 1 locally advanced) with 2 partial responses, and 8 stable diseases. For these 10 patients, the median PFS was 6.5 months and the median overall survival (OS) 9.7 months. For all patients, the median PFS and OS were 2.4 and 8.1 months, respectively. Hematotoxicity was the main side effect. 11 patients (65%) had a grade 3–4 neutropenia, 5 had febrile episodes. One patient died of febrile neutropenia (this patient refused hospitalization). Grade 3 nausea/vomiting occurred in 5 patients and grade 3 diarrhea in 3 patients.

Conclusion: This combination has an acceptable toxicity and interesting results in terms of OS in APC patients. Final results will be presented during the meeting.

Postoperative Radiotherapy ± Adjuvant Systemic Therapy in the Breast Conserving Treatment (pT1/pT2) – Experience of More than 15 Years

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Background: The long-term role of postoperative irradiation with/without adjuvant systemic therapy in routine treatment for breast cancer.

Methods: A retrospective review (1979–1995) of 586 consecutively treated women with breast cancer in stage pT1/pT2 (lost of control 7, radiotherapy stopped 5). Age median 54 (23–92) years, follow-up median 100 (60–258) months.

Results (%): See table 1 (p. 7 top).

Table 1.

Therapy	n	LRFS			DMFS			DFS			CSS			OS		
		5y	10y	15y	5y	10y	15y	5y	10y	15y	5y	10y	15y	5y	10y	15y
RT (pN+: 36.7%)	257	92	90	88	91	84	77	86	78	73	95	87	81	94	83	70
RT+syst. Th186 (pN+: 78%)	317	96	90	87	85	80	80	83	76	74	90	83	73	88	78	62
p-value			0.2			0.09			0.6			0.004			0.03	

Conclusions: Parallel decrease of LRFS in both groups. After 15 years any occurrence of tumor (local/general) was exceptional. In the group with clearly elevated high-risk factors and treated with adjuvant systemic therapy, no difference in LRFS, DMFS and DFS was found, but we observed statistical significant differences for CSS and OS.

Local Dose Escalation with IORT: A Benefit for Local Control and Survival for Retroperitoneal Sarcomas?

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Background: Retroperitoneal soft tissue sarcomas treated by surgical resection alone show high local failure rates (70–80%) and low overall survival rates (OSR). Previous studies observed increased local tumor control rates and better overall survival in patients treated with adjuvant radiotherapy. External beam radiotherapy (EBRT) alone however shows dose limitations because of organs at risk. Additional intraoperative radiotherapy (IORT) gives the possibility for local dose escalation.

Methods: From June 1991 to December 2000 we treated 63 patients with primary (n = 24) or recurrent (n = 39) retroperitoneal soft tissue sarcoma. 17 patients had low-grade and 46 patients high-grade sarcomas. At time of treatment no patient had distant metastases. The treatment included maximal tumor resection, IORT to the high-risk areas, and postoperative EBRT. Resectability: R0 51%, R1 30%, and R2 19%. The mean IORT dose was 15 Gy. 59 patients had postoperative EBRT (36.0–50.4 Gy), 4 patients with recurrent disease had IORT alone due to previous EBRT in the primary situation.

Results: After a median follow-up of 31 months, 36 patients (57%) were alive, resulting in a 5-year OSR of 49%. A significant difference in OSR between low-grade and high-grade lesions (78 vs. 42%) could be observed. Survival was significantly increased after R0 (65%), in contrast to R1 (52%) or R2 (22%) resected patients. The 2-year and 5-year actuarial local control rate for all patients was 78 and 65%, respectively. One patient had postoperative wound complication. Severe acute gastrointestinal side effects were rare (2 patients). Gastrointestinal fistulae or stenosis (3/9 patients), peripheral neuropathy (6 patients), and ureter stenosis (2 patients) were found as late adverse effects.

Conclusion: In this study the combined treatment modality including maximal surgical resection, IORT and EBRT offered by dose escalation an effective method to improve local tumor control, disease-free and overall survival without increased toxicity to normal tissue.

Navigation in der interstitiellen Brachytherapie

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Fragestellung: Das Ziel dieser Arbeit war eine Verbesserung der Genauigkeit der Katheterimplantation in der interstitiellen Brachytherapie. Hierfür wurde ein System zur Echtzeit-Computer-assistierten, 3D-navigierten Nadelimplantation entwickelt.

Material und Methoden: Ein neues Instrument zur navigierten Nadelimplantation wurde mit Unterstützung der Firma Aesculap (Tuttlingen) entwickelt und in die Hard- und Softwareumgebung des SPOCS-Navigationssystems integriert. In einem Planungs-CT eines Phantoms wurden Zielpunkte und der Implantationsweg der Nadeln definiert und die Implantation entsprechend der Planungsvorgabe durchgeführt und mittels eines zweiten CT-Scans bezüglich ihrer Genauigkeit untersucht.

Ergebnisse: Die Genauigkeit der Implantation einer Nadel lag in 50 Versuchen bei 0,9 mm im Zielpunkt, Standardabweichung 0,6 mm, maximale Abweichung 2,3 mm. In einem zweiten Test wurde ein Phantom mit 7 geometrisch angeordneten Zielpunkten konstruiert. Die Gesamtgenauigkeit aller 7 Nadeln in 10 verschiedenen Experimenten betrug 1,6 mm, Standardabweichung 0,7 mm, maximale Abweichung 2,1 mm.

Schlussfolgerung: Echtzeit-3D-Navigation ermöglicht eine genaue, reproduzierbare und verlässliche Platzierung von Brachytherapie-Kathetern.

The Role of Brachytherapy in the Treatment for Localised Prostate Cancer – a Review

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Background: The incidence of prostate cancer increased steadily over the last 10 years. Indeed, a number of treatment options are now available and include radical prostatectomy, external beam irradiation and brachytherapy.

Methods: A review of literature

Results:

Table 1. Range of survival/NED after 5 and 10 years (%)

	Conservative		Prostatectomy		Radiation		I-125 seeds	
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
5 years alive	67.0	92.0	68.9	95.0	51.4	93.0	75.0	93.0
5 years NED	68.0	93.0	81.9	92.0	32.0	93.0	38.0	90.0
10 years alive	34.0	70.7	44.4	88.0	41.4	70.0	50.0	63.0
10 years NED	53.0	81.0	82.0	82.0	40.0	64.0	50.0	90.0

Transperineal, ultrasound-guided brachytherapy with I-125 is most commonly performed as monotherapy. However, brachytherapy may be combined with external beam irradiation.

Table 2. The selection of patients for prostate brachytherapy alone or combination

	PSA, ng/ml	Gleason score	Prostate volume, g	Stage
Monotherapy	≤10	≤6	≤40	≤T2a
Combination	10–20	≤7	40–60	≤T3

Conclusions: The brachytherapy represents an additional therapy option in the management of patients with early prostate cancer and for the high-risk cases adding a boost of external beam irradiation.

First Experiences in the Palladium-103 Brachytherapy for Prostate Carcinoma

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Background: The radiotherapy of the early prostate carcinoma with palladium-103 (Pd-103) brachytherapy can be an alternative to prostatectomy.

Methods: 70–80 Pd-103 seeds are positioned by rectal ultrasound. The pallers are applicated by Mick-Applicator transperineally. The indication is given only in early tumor staging.

Results: The tolerance of brachytherapy with Pd-103 was very good.

PSA before brachytherapy: 2.2–6.0 ng/ml

PSA after brachytherapy: 0.1–2.2 ng/ml

Conclusions: Late side effects of prostatectomy (incontinence, impotence) as well as radiation exposure of the rectum can be reduced.

Metabolic Treatment with ⁹⁰Y-DOTATOC* in 4 Consecutive Cases with Advanced Neuroendocrine Tumors

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(*DOTATOC = Dotecan acetic acid Ty² octreotide)

Introduction: Advanced neuroendocrine tumors are usually refractory to standard chemotherapy. Improving the clinical symptoms is the main therapeutic goal.

Patients and Results: We report on 4 consecutive patients, in whom diagnostic octreotide scintigraphy showed reactivity of the primary tumor and the metastases as well. The patients were treated between 11/1999 and 06/2001. Two to four cycles of ⁹⁰Y-DOTATOC were given; the average dose was 180 mCi per cycle. Only mild gastrointestinal side effects occurred. All patients clinically improved. One female patient had an almost complete regression of the primary tumor located in the pancreas and of multiple metastases in the liver and the spleen. More details on the clinical courses of the patients will be presented at the meeting.

Conclusion: Treatment of advanced neuroendocrine tumors with ⁹⁰Y-DOTATOC is well tolerated. Our experience in 4 consecutive patients suggests that this therapeutic modality is highly effective.