Abstracts

17th Annual Meeting

Oberrheinische Arbeitsgemeinschaft für
Onkologie (OAO)

Groupe de Travail des Oncologues du
Rhin Supérieur (GTOR)

Association for Oncology of the
Upper Rhine (AOR)

Strasbourg, France, February 2–3, 2001

Guest Editor

J. P. Bergerat, Strasbourg, France

ENDOBONCHIAL ULTRASOUND (EBUS) FOR DETECTION OF EARLY LUNG CANCER

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Purpose: Autofluorescence-bronchoscopy (AF) improves detection of early lung cancer. In comparison to histological findings, 20–50% of these lesions are false positive. As by EBUS all layers of the bronchial wall can be differentiated, we investigated its use in diagnosis of those lesions.

Methods: In an ongoing study, evaluating a new AF-method (D-light), EBUS has been used for further characterisation of suspicious lesions. From 4/99 to 8/00, 229 patients were enrolled for examination with AF. EBUS was performed in 50 pts. (20 female, 30 male, mean age 63.3) with suspicious lesions in AF or white-light-bronchoscopy (WLB). Pts. with visible tumors or radiological findings were excluded. EBUS was classified as malignant or benign according to the integrity of the structures of the bronchial wall. The findings were compared to histology.

Results: Histology was malignant in 22 cases (17 NSCLC, 3 SCLC, 2 metastasis) and benign in 28. Malignancies were diagnosed by WLB in 27%, by AF in 63% and by EBUS in 87%. In benign lesions correct diagnosis by WLB was 85%, by AF 77% and by EBUS also 77%. Combination of AF and EBUS improved correct diagnosis up to 92%. No complication related to EBUS was observed.

Conclusion: By imaging the multilayer structure of the bronchial wall EBUS significantly improves results of white-light and autofluorescence-bronchoscopy.

Clinical Implication: EBUS is easily performed. It will play an important role in local staging of small lesions and in some hospitals is already used for planning of endoscopic treatment.

MOLECULAR TARGETED THERAPY IN CHRONIC MYELOGENOUS LEUKEMIA (CML) – CLINICAL EXPERIENCE WITH STI571

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The deregulated tyrosine kinase activity of the BCR-ABL fusion protein has been established as the causative molecular event in CML. STI571 (Glivec[®]) is an ABL-specific tyrosine kinase inhibitor that in preclinical studies selectively kills BCR-ABL containing cells in vitro and in vivo. Phase I results in patients with CML in chronic and advanced phase demonstrated that STI571 is well tolerated and active. Three phase II studies have been designed to further evaluate the efficacy of STI571 in chronic phase (CP) CML patients resistant or intolerant to interferon α , patients in accelerated phase (AP), and in blast crisis (BC). Recruitment for a phase III study comparing STI571 vs interferon α /arabinosyl cytosine standard therapy is ongoing. STI571 is being used at doses of 400–600 mg for chronic phase and 400–800 mg for advanced phase patients. We report on our experience with STI571 in 166 patients (82 CP, 46 AP, 36 myeloid BC, 1 lymphoid BC, and 1 Ph+ acute lymphoblastic leukemia). STI571 is highly active in CP with 95–100% hematological remissions and about 50% major cytogenetic remissions after 6 months of therapy. By sensitive molecular techniques, residual disease has not been eradicated in any patient after a median of 7 months of therapy. Most patients in AP return to CP. In myeloid BC, hematological responses have been observed in 65% of patients. However, responses are durable only in a minority of BC patients. Therefore, the need for combination and/or consolidation therapies will be addressed in future studies. Common non-hematologic side effects consist of mild to moderate fluid retention, gastrointestinal discomfort, and muscle cramps. Prolonged myelosuppression has been observed in patients with advanced Ph+ leukemias.

The development of STI571 represents a new paradigm in cancer drug development. Results of clinical studies have demonstrated the potential of molecularly targeted therapies and STI571 is emerging as an important new therapeutic agent for CML.

PROGNOSTIC FACTORS AND THE NEED FOR RADICAL SURGERY IN PATIENTS WITH EARLY GASTRIC CANCER?

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Background: Today most surgeons in the western world perform subtotal or total gastrectomy in cases of early gastric cancer (EGC) with respect to tumor localization. Two issues are still a matter of debate among surgeons, on the other hand. First, is extended systematic lymphadenectomy necessary and second, is limited resection of EGC oncologically sufficient.

Patients und Method: Data of patients with gastric cancer prospectively collected since 1972 at our hospital, were reviewed for patients with cancer confined to the mucosa and submucosa of the stomach (EGC). Probability of survival with reference to T-stage, nodal status, and histologic characteristics was calculated using the Kaplan-Meier method.

Results: 260 patients with pT1 gastric cancer were operated between 1972 and 1999. These patients were subject to either subtotal or total gastrectomy and systematic lymphadenectomy (D1).

The cumulative probability of survival after 10, 15 and 20 years was 65 percent, 52 percent and 42 percent, respectively.

There was no statistically significant difference in long-term survival with respect to T-stage (T1a or T1b), nodal involvement (N0 or N1), grading, or type of surgery (total vs. subtotal gastrectomy). Patients with intestinal type cancer had a better prognosis than those with diffuse or mixed type cancer.

Conclusion: Considering the frequent incidence of lymphatic spread in early gastric cancer penetrating the submucosal layer (sm), we advocate total or subtotal gastric resection with respect to tumor localization and systematic D1-lymphadenectomy in patients with EGC. Adequate surgical treatment provides excellent long term survival in these patients.

DOWNSTAGING ADVANCED RECTAL CANCER BY PREOPERATIVE CHEMORADIO THERAPY

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Rationale: Locally advanced tumors of the rectum often recur locally or cannot be operated by sphincter sparing procedures. Several studies have shown that preoperative chemoradiation improves local control survival and operability.

Methods and Materials: In the years 1994 to 2000 we treated 36 patients (25 men, 11 women) by preoperative radiotherapy. The median age was 64 (range 24-83). The tumor stages were uT3 (N=2), uT4 (N=11) and cN1 (N=12), cN2(N=1). The histological grade was G1 (N=4), G2 (N=23), G3 (N=4), GX (N=5). The location of the tumor was in 53% (19/36) closer than 6 cm of the anus, which was considered critical for sphincter saving surgery. In 32 cases the patients got simultaneously chemotherapy of 5FU. Eight regional oncology centers administered chemotherapy which was given continuously in 30 cases at dose of 200 or 225 mg/m²/day over 5 weeks. In the early years no chemotherapy was given in 4 cases or in 2 cases over 2×5 days 4 weeks apart with a dose of 1000 mg/m²/day. Radiation was given in prone position with a 3 field technique encompassing the whole pelvis on a belly board. For all patients the total dose was 45 Gy with the dose prescribed to the isodose and a daily fraction of 1.8 Gy. Surgical resection was carried out 23–74 days later (median 38 days).

Results: All patients finished the planned radiation and chemotherapy timely (median 35.5 days, range 32–39). The median time from diagnosis to start of radiation was 27 days (range 8–119). 1 patient refused operation and 1 patient left for Spain and was lost. In 20 patients a sphincter sparing resection was possible, whereas 7 cases were with tumor location initially closer than 6 cm. 14 patients underwent abdominoperineal resection. The resection was in 3 cases not locally radical (R1). Downstaging was possible in 59% (20/34) for T stage, in 54% (7/13) for N+ cases. Upstaging was necessary in 5 cN0 cases to pN1 and in 2 cases to pM1(hepar). Histology revealed in 21% no tumor.

SENTINEL NODE BIOPSY (SNB) IN VULVAR CANCER

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Introduction: The feasibility of SNB and its contribution to the reduction of postoperative morbidity were prospectively evaluated.

Methods: Between July 1998 and July 2000, 12 females with invasive vulvar cancer (4 T1No, 6T2No squamous cell carcinomas, 2 melanomas) were entered in the study. Median age was 66 years (range: 22–78). Sentinel lymph node (SLN) was detected by Patent Blue dye (GUERBET, FRANCE) in one case, radiopharmaceutical (14.8 MBq 99m Sulfur Colloid, NANOCIS, FRANCE) in 3 cases, and combined techniques in 8 cases. Pre-operative lymphoscintigraphies were performed at 30 and 120 min. An intra-operative gamma probe (NAVIGATOR, TYCO, USA) was used to identify the SLN. All SLN were investigated by permanent routine H-E staining, serial sectioning, immunohistochemistry and intra-operative imprint cytology for the last cases of the series.

Results: SNB was successful in all cases but 2 (83.3%). Median number of SLN removed was 1.5 (1–3). SLN was invaded in 3 cases (30%) and confined to the SLN in 2 patients. Primary tumor was treated by radical (10 cases), partial vulvectomy (1 case) or wide excision (1 case). Selective lymphadenectomy (SNB alone) was performed in 7 cases and completed by inguinofemoral (4 cases) or superficial inguinal lymph node dissection (1 case). No specific morbidity and distant sequelae related to SNB were observed. The median follow-up was 17 months (range: 1–26). The local recurrence rate was 8.3% (1/12) related to SLN misidentification. In spite of a bilateral superficial inguinal clearance, one patient recurred medially at 6 months and died at 8 months from brain failure without evidence of metastasis.

Conclusion: Demonstrated as a feasible and promising minimally invasive tool, SNB requires further evaluation before being considered as a reliable standard procedure in patients with early vulvar cancer.

DEXAMETHASONE PULSE THERAPY (DPT) IN PATIENTS WITH CHLOR-AMBUCIL-REFRACTORY CLL – LONG-TERM FOLLOW-UP IN SELECTED CASES

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In patients with chlorambucil-refractory CLL usually nucleoside analogs are the treatment of choice. However, in patients with hemolysis it is cautioned to treat with fludarabine.

We report on 9 patients with chlorambucil-refractory CLL. 8 patients had signs of hemolysis and/or idiopathic thrombocytopenic purpura. 1 further patient was heavily pretreated (inclusive pentostatin) because of lymphoid masses. All patients were treated with DPT in 2–4 week intervals. Dexamethasone was given in a dose of 40 mg p.o. days 1–4. The response duration is up to 72 months.

2 patients developed pneumocystis carinii pneumonia – 1 of whom died. 8 patients are alive. More detailed information on the clinical course of all 9 patients will be given at the meeting.

In conclusion these selected cases show that in patients with chlorambucil-refractory CLL with signs of hemolysis it is worthwhile to try DPT.

SIGNIFICANTLY INCREASED ANGIOGENESIS IN MYELOPROLIFERATIVE DISORDERS

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Angiogenesis is crucial for growth of solid tumors, but very likely is also involved in the pathogenesis of a variety of hematological diseases. Thus, an increased bone marrow angiogenesis has been found in AML, ALL, multiple myeloma, CML (chronic phase), polycythemia vera (PV) and osteomyelofibrosis (OMF).

Therefore we wanted to investigate whether patients with advanced CML (accelerated phase, and blast crisis) or

essential thrombocythemia (ET) have an increased bone marrow angiogenesis and if treatment with interferon alpha that can inhibit angiogenesis in hemangiomas results in a decrease of bone marrow angiogenesis in patients with myeloproliferative disorders.

In total, we studied 68 patients with myeloproliferative disorders that included 6 patients with CML-accelerated phase, 7 patients with CML-blast crisis and 15 patients with ET, as well as 19 patients with CML-chronic phase, 17 patients with PV, 4 patients with OMF, and 30 normal individuals as controls. The bone marrow angiogenesis was determined by counting the microvessels in bone marrow biopsies thin sections after staining of the microvessels with CD34 or von Willebrand factor antibodies.

The median microvessel density in the bone marrow of normal individuals was 3.7 per mm². In the bone marrow of all myeloproliferative disorders, a significantly increased bone marrow density was detected: in CML-chronic phase, the median microvessel density was 9.0 per mm² (p=0.0004), in CML-accelerated phase 10.4 per mm² (p=0.0071), in CML-blast crisis 9.3 per mm² (p=0.0047), in PV 8.5 per mm² (p=0.016), in ET 7.7 per mm² (p=0.0006) and in OMF 11.7 per mm² (p=0.05). 5 patients with ET who received interferon alpha at a dose of 9 million units per week did not differ significantly in the microvessel density when compared to untreated patients with ET; in contrast, 3/4 patients with CML-chronic phase, who received 42 million units of interferon alpha per week, had a significantly lower microvessel density (p=0.0004) when compared to patients with CML-chronic phase at diagnose.

We conclude that i) all myeloproliferative disorders are associated with an increased microvessel density and ii) that a medium dose of interferon alpha seems to inhibit angiogenesis in patients with CML-chronic phase. The increased microvessel density in myeloproliferative disorders may be involved in the pathogenesis of these diseases.

INCREASED LEVELS OF BFGF MRNA TRANSCRIPTS IN PH-NEGATIVE CHRONIC MYELOPROLIFERATIVE DISORDERS BUT NOT IN CHRONIC MYELOGENOUS LEUKEMIA

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Bone marrow (BM) vascularity is increased in polycythemia vera (PV), chronic myelogenous leukemia (CML) and myelofibrosis (MF). Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are angiogenic growth factors involved in the regulation of bone marrow vascularisation. We established a quantitative real-time PCR based on the LightCycler technology using specific hybridization probes to determine the amount of mRNA for bFGF and the isoforms of VEGF (VEGF-121 and VEGF-165) in BM. The absolute amount of mRNA transcripts was determined by coamplification of specific plasmid dilution series. Results were standardized for different sample qualities by quantifying glucose-6-phosphate dehydrogenase (G6PD) mRNA transcripts. 37 BM aspirates derived from patients with ET (n=12, 8/12 untreated), PV (n=10, 6/10 untreated), CML (n=17, 8/17 untreated), MF (n=5, 5/5 untreated), and healthy controls (C) (n=12) were investigated. We found a significant increase of the ratio bFGF/G6PD mRNA in ET (med. 0.23, range 0.032–1.2; p<0.0001), PV (med. 0.19, range 0.01–1.8; p<0.0003) and MF (med. 0.3, range 0.18–0.52, p=0.0012) vs C (med. 0.004, range 0–0.064). RNA and cDNA quality was equal for all cohorts, as determined by G6PD-mRNA-levels. Levels for VEGF-121/G6PD and VEGF-165/G6PD were not different between patient cohorts and C. Only in MF VEGF-121 is expressed in a significant lower level.

Ratio	bFGF/G6PD			VEGF-121/G6PD			VEGF-165/G6PD		
	median	range	p	median	range	p	median	range	p
ET (n=12)	0.23	0.032–1.2	<0.0001	7.14	1.01–18.7	0.09	1.67	0.53–18.9	0.11
PV (n=10)	0.19	0.01–1.8	<0.0003	3.96	0.59–8.69	0.07	1.79	0.33–4.35	0.1
MF (n=5)	0.3	0.18–0.52	0.0012	2.37	1.96–4.15	0.02	1.08	0.46–3.53	1.0
CML (n=17)	0.012	0.0–0.39	0.47	4.76	1.9–43.7	0.24	1.33	0.22–2.4	0.14
Contr. (n=12)	0.004	0.0–0.064		9.41	1.69–91.3	0	3.27	0.5–18.9	

This data demonstrates (i) the efficacy of a novel method to determine the expression of cytokines on mRNA level, and (ii) the activation of the angiogenic/fibrogenic system in Ph negative chronic myeloproliferative disorders (CMPD) but not in CML. This might indicate a differential activation of angiogenesis in Ph positive and negative CMPD.

TIMP-1 EXPRESSION ANALYSIS IN RENAL CELL CARCINOMA USING TISSUE MICRO-ARRAYS AND THE LIGHTCYCLER SYSTEM

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Identification and evaluation of molecular parameters is of utmost importance in cancer research and cancer treatment. To identify genes with relevance for renal carcinoma (RCC) progression, a cDNA array analysis was performed on Human Atlas Cancer 1.2 cDNA microarrays with 1176 genes. cDNA from 4 RCC tumor cell lines and 2 renal carcinoma tissues were compared to normal kidney cDNA to screen for genes with differential expression. 43 differentially expressed genes were identified. TIMP-1, a matrix-metalloproteinase inhibitor supposed to be a key player in the regulation of the invasive and metastatic behavior of cancer cells, was strongly expressed in all 6 tumors but only weakly detectable in normal kidney tissue. A renal cancer tissue microarray was immunohistochemically analyzed with a TIMP-1 antibody (clone 147-6D11, Oncogene Research products) to study the prevalence of TIMP-1 expression. TIMP-1 was expressed in 373 of 383 clear cell RCC (97.8 %), all papillary RCC (n=57), all chromophobe RCC (n=23), oncocytoma (n=17) and collecting duct RCC (n=3). As real-time PCR allows precise quantification of gene expression, TIMP-1 expression was further determined in 32 fresh frozen RCC with clinical follow-up information and 6 normal renal tissues using the LightCycler system with GAPDH as external control. 13 RCC (41%) showed a 2–8 fold increased expression level of TIMP-1 compared to normal tissue. 18 RCC (56%) displayed normal and one RCC (3%) reduced TIMP-1 expression. 4 of 13 patients (31%) with increased, but only 2 of 18 patients (11%) with normal TIMP-1 expression died from metastatic

disease. These results indicate a possible relationship between high TIMP-1 expression and metastasis of RCC.

HEREDITARY PREDISPOSITION TO RENAL CANCER: SOME CLINICAL CASES

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Kidney tumours are sometimes observed in several persons within a family or a patient may develop two or more primary kidney tumours. Such situations raise the hypothesis of an hereditary predisposition to kidney tumours. Von Hippel-Lindau disease is a classical predisposition to kidney cysts and renal cancer and associates extra-renal manifestations like hemangioblastomas of the cerebellum, of the spinal cord or of the retina; cysts of the pancreas are also frequent. Hereditary kidney cancer may present as an autosomal predisposition to clear-cell renal cancers. Linkage analysis with probes of the VHL region on chromosome 3 in two families (one Alsacian and one Australian) demonstrated that this genetic condition was distinct from the Von Hippel-Lindau disease. The genetic support for this predisposition is not known.

The t(3;8) translocation was shown by Cohen et al. in 1979 to predispose to renal cancer in one unique large family. The same translocation has been observed in a 34-year-old patient who presented five simultaneous primary renal cancers affecting both kidneys. This translocation is thought to affect the anti-oncogene TRC8.

Renal carcinoma is also part of the spectrum of Cowden disease, like breast and thyroid cancer, lipomas and other cutaneous and mucosal manifestations.

Supernumerary nipples have been linked to an increased frequency of renal malformations and tumours.

Multiple renal tumours in a patient or in a family should prompt an etiological work-up in the probant comprising a full clinical examination, retinoscopy, an MRI of the central nervous system, an abdominal CT-scan, karyotype analysis and, if possible, a molecular analysis of the VHL gene. Persons with an hereditary risk of renal cancer should get yearly imaging of the kidneys. Renal tumours greater than 3 cm in size in this background need to be removed using kidney-sparing surgery.

ADJUVANT RADIO-CHEMOTHERAPY IN STAGE II-III RECTAL CANCER WITH 24-HOURS-INFUSION OF HIGH DOSE 5-FLUOROURACIL AND FOLINIC ACID: EVALUATION OF FEASIBILITY

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Background: In the last decade postoperative radio-chemotherapy has been established as standard treatment for stage II and III rectal cancer patients. To improve the efficacy of this therapy we decided to evaluate continuous 24-hour 5-fluorouracil (5-FU) with folinic acid (FA) in combination with local irradiation in a pilot study.

Patients and Methods: Patients with stage II and III rectal cancer received postoperatively via a port-A-cath system weekly 2 hours infusion of FA 500 mg/m², followed by continuous 24-hour infusion of 5-FU 2,600 mg/m². During the first cycle 8 consecutive weekly administrations were administered, the first to fourth in full dose, the fifth to eighth with reduced dose (50%), while local irradiation was performed (45 and 50.4 Gy, respectively). Thereafter two further chemotherapy cycles followed.

Results: 28 patients were enrolled in this study, of whom 21 were evaluable. 19 patients (90.4%) completed the first cycle, only 14 patients entered the second treatment cycle. Especially during the combined radio-chemotherapy substantial toxicity was observed with grade III/IV diarrhea (n=2), nausea (n=1), leucopenia (n=1) and cardiac toxicity (n=1).

Conclusion: The high rate of patients to drop out of treatment prematurely indicate that the chosen schedule of weekly continuous high dose 5-FU/FA and combined postoperative radiotherapy is not recommended for further use.

SUCCESSFUL TREATMENT OF MERKEL CELL CARCINOMA WITH 90-YTTRIUM-DOTATOC: A CASE REPORT

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Merkel cell carcinomas (MCC) are uncommon, highly malignant skin tumors with a very aggressive clinical course, similar to small cell lung cancer. They develop in sun-exposed areas of the skin, mostly in elderly patients. In addition to frequent locoregional recurrences there is a high incidence of distant metastases. Treatment consists of operation and aggressive adjuvant chemo- and/or radiotherapy. The advanced age of patients often impedes adequate therapy. Since MCC belong to the family of neuroendocrine tumors they also express somatostatin (SMS)-receptors.

90Y-DOTATOC is a novel radiolabeled somatostatin-analogue, containing the active octapeptide of somatostatin. It is very well tolerated and offers the option of treating SMS-receptor positive tumors by targeted radiotherapy. We report on a 83-year-old woman with recurrent MCC of the left cheek. The primary tumor was treated with local operation. Several relapses required additional operations as well as locoregional radiotherapy with 55 Gy. When she presented with the 3rd relapse she was treated with 2 cycles of 85 mCi 90Y-DOTATOC. The tumor disappeared completely after 1 cycle. However, a relapse occurred 3 months later and she was retreated with 90Y-DOTATOC, resulting in a second complete remission. A second relapse was found 1 month later. A 4th cycle of 90Y-DOTATOC was ineffective and conventional chemotherapy was started. There were no side effects of the 90Y-DOTATOC-therapy. Throughout the treatment the MCC remained SMS-receptor positive.

Conclusion: Due to its good tolerability 90Y-DOTATOC should be evaluated further as a new therapy for somatostatin-receptor positive MCC.

COMBINATION OF IRRADIATION AND BISPHOSPHONATES IN THE THERAPY OF BONE METASTASES

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Introduction: The aim of this study was to examine whether the osteoprotective effect of bisphosphonates (BP) can further enhance the therapeutic effect of irradiation in metastatic bone disease.

Material and Methods: Experimental bone metastases were induced in male Wistar rats (200 g) by intraosseous injection of 2×10^6 cells of the Walker CS 256 B in both proximal tibia metaphyses. Three groups, each consisting of 15 animals were studied. All animals were irradiated with a single dose of 17 Gy (6 MeV electrons) at day 7 after tumor injection. The first group received only irradiation, serving as control, the groups two and three were given additionally BPs at days 3–6 (early) or days 7–10 (late) after tumor injection respectively. As bisphosphonate (BP) clodronate (20 mg/kg/d) was used. 5 weeks after tumor injection all animals showed a stable recalcification. The animals were examined 7 weeks after tumor injection. Bone density and bone structure were analyzed using quantitative radiology and bone histomorphometry. Quantitative radiology was performed using x-ray absorption measurements. Bone histomorphometric analysis was performed according to the guidelines of the American Society of Bone and Mineral Research (ASBMR). The parameters bone density and trabecular connectivity were assessed.

Results: Bone density measured by x-ray absorption was significantly higher in early BP treated animals compared with control ($p=0.008$) whereas late administration of BP had no such effect ($p=0.69$). Bone histomorphometric analysis showed significantly higher bone density ($p<0.001$) in early BP treated animals (34%) compared to control (16.1%) and the late BP treated group (20.6 %). Analysis of trabecular intersections revealed trabecular branching to be 43.6 % higher in early BP-treated animals as compared to control.

Conclusions: The therapeutic effect of radiotherapy on bone metastases could not be further improved by simultaneous or late BP treatment. Bone density and structural parameters of bone were significantly higher when BPs

were given early in metastatic development. This study does not support the benefit of a general combination of BPs with irradiation in metastatic bone disease, but the osteoprotective effect of an early BP administration can preserve the structural integrity of the bone and may therefore facilitate a more physiologic rebuilding of osteolytic bone lesions after successful radiotherapy.

LOSS OF QUALITY OF LIFE BY EMOTIONAL DISTRESS IN PATIENTS WITH BONE METASTASES UNDERGOING RADIOTHERAPY

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Objective: To optimize the quality of life for palliatively treated patients therapy-caused and furthermore emotional distress have to be taken into account. In this prospective trial we examined pain relief and satisfaction of patients undergoing radiotherapy of bone metastases.

Methods: Between 6/99 and 06/00, 84 patients with symptomatic bone metastases were included prospectively into this trial. Inclusion criteria were: symptomatic bone metastases; outpatient treatment; Karnofsky Index $>70\%$; breast, prostatic or lung cancer as primary tumor; standard radiotherapy procedure (total dose 40 Gy). The following parameters were inquired about: (1) Pain relief, (2) organizational requirements and resulting distress, (3) duration of journey, (4) distress caused by waiting time and (5) distress caused by radiation procedure, (6) significance of radiotherapy to the patient, (7) overall patient satisfaction.

Results: (1) All patients had painful metastases at start of treatment, 6 weeks after therapy 84% of the patients had a significant pain reduction, 26% of these patients were without pain. Reduction of pain medication ($>50\%$) occurred in 79.2% of the patients, 47.9% of these patients were without medication. (2) Strain by organizational requirements: 60% of patients (85% of women). (3) Duration of journey one way: $\varnothing$ 45 min. (4) Strain by waiting time: 67% of patients (34% very straining). (5) 34% of patients felt strained by the actual radiotherapy procedure. (6) Significance of radiotherapy to the patient (multiple answers were possible): healing (85.4%), reduction of pain (49%), an alternative to chemotherapy (14.5%), a delay in the progress of disease

(5.5%) or an extension of survival (5.5%). (7) 70.9% of the patients were satisfied with the treatment, 98.1 % of all patients would again choose radiotherapy for treatment.

Conclusions: In addition to the known very effective pain reduction and the high general patient satisfaction, radiation therapy still resulted in distress for patients during therapy mostly due to non-medical organisational reasons. Further improvement of quality of life may be achieved by optimizing the course of treatment and an expanding caring for patients in the clinic.

THE TREATMENT OF POOR PROGNOSIS ARTERIOVENOUS MALFORMATIONS BY RADIOSURGERY. THE NANCY EXPERIENCE FROM 1992 TO 1998

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Methods: From July 1992 to July 1998, 118 patients (55 male, 63 female) were treated for an ArterioVenous Malformation (AVM) by a single fraction Linac radiosurgery. The mean follow-up was 37 months (5–91) with 4 patients lost to follow-up. The mean age was 35 years (14–66). All AVM had poor prognosis features at initial presentation: high Spetzler-Martin grade (67% of grade III or higher: 59/88), big size (57% of principal diameter bigger than 30 mm) and the high rate of initial hemorrhage (53%: 62/118). Patients had already been treated in 85% of cases (100/118), 81% by embolization (mean number of 4 procedures), 3% by partial surgery and embolization and 1% by partial surgery alone. Radiosurgery consisted in the irradiation of one target in 107 patients (90 %), two targets in 9 patients (8%), three targets in 2 patients (2%). All the targets were irradiated with a single isocenter. The mean size of the single targets was 22 mm (8–31). The mean minimal dose was 17 Gy (10–25) and the mean maximal dose 24 Gy (16–36). **Results:** A cure of the AVM was observed in 57 of the 102 patients evaluated (56%). Cure was defined on angiographic (100) or MRI (2) appearances. The only prognostic factor of cure found in a multivariate analysis was the small principal diameter of the AVM ($p=0.0001$; OR=0.79 [0.70–0.89]) with a cut-off at 21 mm (83% (32/37) vs. 44%

(22/50); $p < 0.001$). 4 patients had acute (first three months) complications (transitory confusion, transitory facial peripheral palsy, definitive scotoma, permanent paralysis of the III nerve). 6 patients had late complications due to radionecrosis (5 patients developed a transitory deterioration of epilepsy or other neurological deficit, 1 patient developed a permanent hemiparesis). 6 patients had a subsequent hemorrhage after radiosurgery with a mean time of 3 years (1–6.5). Following the hemorrhage, 2 had spontaneous occlusions of the AVM, 2 had successful occlusions with further treatment and 2 had no cure of the AVM despite further treatment. All the patients who achieved either a cure (57 pts) or an occlusion of more than 95% of the initial volume of the AVM (14 pts) were free of subsequent hemorrhage. The annual risk of hemorrhage in absence of cure was 3.85% (3.82–3.88).

Conclusion: Our study confirms the place of radiosurgery as an efficient treatment of poor prognosis AVM with a low rate of complications. The rate of hemorrhage after radiosurgery is low, nil after cure or achievement of a volume reduction of more than 95%. In cases of unsuccessful treatment or during the time between treatment and occlusion, the hemorrhage rate seems to be comparable to the one observed in untreated AVMs.

EFFICACY OF EXTERNAL FRACTIONATED RADIOTHERAPY IN THE TREATMENT OF INTRACRANIAL MENINGIOMAS: A 20-YEAR EXPERIENCE AT CENTRE ALEXIS VAUTRIN, NANCY

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Introduction: We report our experience in the treatment of intracranial meningiomas in adults over the past 20 years. Our purpose was to assess the efficacy of this treatment modality in terms of local control and survival.

Material and Methods: From 1978 to 1997, 45 patients were referred to our institution for external fractionated radiotherapy. Initial diagnosis was assessed by histological analysis in 36 patients and based upon clinical and radiological criteria in 9 non-operated patients. Among the 33 available pathology reports, 26 benign (79%), 2 atypical (6%)

Table 1. Local control and overall survival (median follow-up: 30 months, range 1–166)

	n	5-yr. LC	8-yr. LC	5-yr. OS	8-yr. OS
All patients	45	75%	67%	74%	74%
Benign lesions*	26	95%	81%	85%	85%

LC = Local control; OS = Overall survival; *: histological data available.

and 5 malignant (15%) lesions were recorded (WHO classification).

Radiotherapy was performed postoperatively after a first subtotal resection in 11 cases, at the time of first recurrence in 14 cases ($\pm$ salvage surgery), as salvage treatment (for the second or a subsequent recurrence, $\pm$ salvage surgery) in 11 cases, as exclusive treatment in 9 cases. Radiotherapy dose to the tumor bed (I.C.R.U.) was 50–59.2 Gy in 30 patients and 60–70 Gy in 15 patients (median 56 Gy), 1.8–2 Gy per fraction, 5 days a week. From 1995 to 1997, 19 patients were treated using a 3-D conformal technique.

Results: With a 30-month median follow-up (range 1–166), computed results in terms of local control and overall survival are reported in table 1 for all patients and pathologically confirmed benign lesions. No major radiation-induced complication occurred in our series.

Several factors were tested to assess their prognostic significance. Neither radiotherapy dose (≥ 60 Gy vs. < 60 Gy, $p=0.60$) nor patient age at the time of irradiation (≥ 60 vs. < 60 , $p=0.25$) influenced local control or overall survival. On the other hand, atypical and malignant lesions had worse prognoses in terms of local control and overall survival than benign ones ($p < 0.01$).

According to radiotherapy indication, we split our series into 4 indication groups :

- after postoperative irradiation, local control was 90% (median follow-up: 45 months);
- after first recurrence, 73% (median follow-up: 35 months);
- after the second or a subsequent recurrence 67% (median follow-up: 22 months);
- as exclusive treatment, 80% (median follow-up: 45 months).

The results yielded in these groups were not statistically different.

Conclusion: Our results compare favorably with those previously published. External radiotherapy is safe and effective, providing 70–80% 5-year local control for the whole series and more than 90% 5-year local control for benign lesions with no or little morbidity. We are now using a 3-D conformal technique to optimise our treatments.

Authors are still debating about the place of radiotherapy in the treatment of meningiomas: after subtotal resection, should radiotherapy be applied postoperatively or at the time of progression? Should radiotherapy replace surgery when the risk of postoperative sequelae is high? Prospective randomised trials would be required to address these issues.

HTLV-1 ASSOCIATED PLEOMORPHIC LARGE T-CELL LYMPHOMA. COMPLETE REMISSION AFTER STANDARD CHEMOTHERAPY MAINTAINED WITH LAMIVUDINE/ ZIDOVUDINE. A CASE REPORT FROM THE BASEL LYMPHOMA CONFERENCE

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Between 1995 and 2000, the Basel Lymphoma Conference registered 225 consecutive new patients with Non-Hodgkin's lymphomas, 7% ($n=15$) of whom belong to the group of lymphomas that are, at least in part, considered to be associated with a viral agent (EBV: $n=8$ {immunosuppression associated: $n=6$, CNS: $n=2$ }, HIV: $n=6$, HCV: $n=1$). It still remains unclear, whether the respective virus is the causative agent of these lymphomas.

Only a small fraction of malignant lymphomas is clearly induced by a known infectious agent. One of these is *Helicobacter pylori* causing MALT lymphoma of the stomach ($n=2$), and a second is HTLV-1, a virus which is endemic mainly in Western Africa, the Caribbean and Southern Japan.

We report on a 51 year old male patient of West African origin who presented with cervical adenopathy and weight loss and was found to have disseminated disease with bulky

abdominal lymphomas and infiltration of the spleen and the bone marrow. His serum LDH was 3950 U/L (no: < 425). His International Prognostic Index risk score was 'high intermediate'. The cervical biopsy showed a large T-cell lymphoma. He was not HIV-infected, but had antibodies against HTLV-1, confirmed by Western Blot. He received 8 cycles of CHOP and was in CR after 6 cycles. No CNS prophylaxis or radiation was given. He has no HLA identical siblings, so he was no candidate for allogeneic transplantation. To suppress possible HTLV-1 activity, an antiretroviral regimen with Lamivudine/Zidovudine was given. He remains in complete remission.

The patient's wife, who is a native of Switzerland, was also found to be positive for HTLV-1.

Consecutive HTLV-1 viral load data will be shown. The consequences regarding HTLV-1 blood transfusion testing and the options regarding family counseling will be discussed.

PHASE II STUDY OF WEEKLY 24-HOUR INFUSION OF HIGH-DOSE 5-FLUOROURACIL (HD-5-FU) PLUS FOLINIC ACID (FA) IN COMBINATION WITH 3-WEEKLY MITOMYCIN C (MMC) IN ADVANCED GASTRIC CANCER (AGC)

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Background: Recently HD-5-FU with FA has yielded high response rates in the treatment of AGC, and mitomycin is known to be one of the most active single agents in AGC. We investigated the combination in a phase II trial to improve outcome in terms of response and survival.

Patients and Methods: Since 8/98 we have recruited 34 patients (pts) with metastatic or recurrent AGC in a single institution. So far 30 pts are evaluable for interim analysis: 13 m / 17 f, median age 56.5 y (28–76); 10 adenocarcinomas of the esophagogastric junction, 20 corpus/antrum; ECOG-status: 0: 9pts, 1: 18pts, 2: 2pts, 3: 1pt. 13 pts with liver metastases, 5 with peritoneal carcinomatosis, 13 lymph-node metastases. Treatment schedule: MMC 10 mg/sqm days 1+22, and 6 weekly infusions of FA 500 mg/sqm followed by a 24-hour infusion of 5-FU 2600 mg/sqm. One cycle equals 8 weeks. Treatment was given in an outpatient setting via i.v.-port and portable pump system.

Results: A median 92.4% of the planned MMC- and 83% of the 5-FU-dose was given. Toxicity (67 treatment cycles evaluated) was mild: 10% leucopenia 3°, 6.7% thrombopenia 3°, 3% diarrhea 3°. One pt developed hemolytic-uremic syndrome grade 4° several weeks after the last MMC-application. Thus, an association with MMC is questionable. No further grade 4 toxicities were observed. Efficacy (28 pts with measurable disease): 3 CR, 12 PR (ORR 54%), 8 NC, 5 PD. Median time to progression was 6.6 months and median overall survival was 10.1 months.

Conclusion: MMC + HD-FU/FA is a low-toxic regimen showing high activity being in the upper range of comparable regimens.

GEMCITABINE IN HORMONE-REFRACTORY PROSTATE CANCER PATIENTS

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Background: Hormone-refractory prostate cancer is characterized by a low response rate at second-line therapy. Gemcitabine is a pyrimidine analogue with a broad spectrum of antitumor activity mainly against solid tumors. This agent is well tolerated with a mild toxicity profile.

Patients: Twelve patients with hormone refractory prostate cancer were treated with Gemcitabine 1000 mg/m² (infusion within 30 min) every two weeks. 8/12 patients had also received radiotherapy prior chemotherapy. Ages ranged from 53 to 80 years. The treatment was continued until progression occurred.

Results: In two patients we documented a dramatic decrease of PSA: 94 and 45% from baseline. Response duration was 12 and 5 months, respectively. One patient showed stable disease for a period of 12 months. Three additional patients had a transient regression of previously enlarged lymph nodes.

The biweekly schedule was well tolerated. No severe hematological side effects were seen. Most of the patients experienced mild fatigue and asthenia the days following chemotherapy.

In conclusion Gemcitabine is well tolerated and moderately active in hormone refractory prostate cancer.

CARDIAC MANIFESTATION IN HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL) – REPORT ON TWO CASES

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Background: Intracardial growth of NHL is occasionally seen late in the course of the disease. We report on 2 cases with high grade NHL in whom intracardial growth was the leading manifestation of the disease.

Patients: *Case 1:* A 66-year-old man was admitted to the local hospital with chestpain, pain to the left arm and with mild dyspnea. On echocardiography a solid mass in the atrium was seen. The patient underwent cardiac surgery. The tumor was completely resected; it had spread from the mediastinum to the right atrium and to the aortic wall. On histologic examination the diagnosis of a high-grade NHL was made. The staging examinations revealed no other manifestations (stage I E). After surgery the patient received 3 cycles of CHOP and the mediastinum was irradiated (36 Gy).

Case 2: A 77-year-old woman developed a third degree AV block in February 2000; a pacemaker (DDD) was implanted. Three months later an intra-atrial mass was detected on routine echocardiography. Further clinical examination revealed an enlarged lymph node in the neck which was resected. The pathologic diagnosis was: high-grade NHL. No other manifestations were found (stage II E). From beginning of June to the end of August 5 cycles of CHOP were given.

Results: Right now both patients are in complete remission.

Conclusion: Primary cardiac Non-Hodgkin's lymphomas are rare. In the literature most cases are from Japan. Therapeutic guidelines are not available. Our data suggest that CHOP +/- irradiation is effective.

PARANEOPLASTIC LIMBIC ENCEPHALOPATHY IN A PATIENT WITH NON-HODGKIN'S LYMPHOMA (NHL) – A RARE DIFFERENTIAL DIAGNOSIS OF STUPOR

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Background: Mental impairment is often seen in patients treated for malignant disorders. Paraneoplastic limbic encephalopathy is a rare differential diagnosis in these patients.

Patients: We report on a 63-year-old patient that presented to our hospital with a 1 week history of progressive gait ataxia and stuttering. She was disorientated and showed signs of a delirious organic psychosis. During the following hospital course she developed episodes of stupor and catatonia that were accompanied with high-grade fever and tachycardia. 4 years earlier the patient had been diagnosed with Mantel Cell lymphoma (centrocytic lymphoma) and was treated with 6 cycles of fludarabin. After achieving a complete remission she was put on maintenance therapy with alpha-interferon. At the current presentation a relapse with a marked lymphocytosis could be diagnosed. After CT and MRI studies of the brain and an examination of spinal fluid were nondiagnostic, paraneoplastic limbic encephalopathy was diagnosed and chemotherapy (cladribine) was started.

Results: The patient did not respond to this therapy and chemotherapy was changed to CHOP. Already after the first cycle the patient's condition improved rapidly with cessation of the stuporous episodes. After 6 cycles of chemotherapy the neurological und psychiatric symptoms had disappeared completely. The patient is currently doing well with a good partial haematological remission 6 month after salvage therapy.

Conclusions: Paraneoplastic limbic encephalopathy is a rare disorder that should be considered in the differential diagnosis in patients with mental impairment and underlying malignant disease.

An overview of the differential diagnosis of stupor and of paraneoplastic syndromes in patients with NHL will be given.

CHEMOTHERAPY ASSOCIATING OXALIPLATIN-5FU AND FOLINIC ACID IN HEAVILY PRETREATED METASTATIC BREAST CANCER

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Objective: Retrospective study of the concurrent administration of oxaliplatin-5FU-folinic acid in the treatment of metastatic breast cancer.

Patients and Methods: 14 patients between 32 and 70 years of age were treated from 1998 to May 2000 with oxaliplatin 100 mg/m² IV over 3 h on D₁, folinic acid 500 mg/m² IV over 2 h on D₁ and D₂, 5FU 1.5 g/m² IV over 22 h on D₁ and D₂. This treatment was administered on average as a 4th-line metastatic therapy (2–7). All patients had prior treatment with 5FU and anthracyclines either as adjuvant therapy, neoadjuvant therapy, and/or metastatic therapy. A taxane was previously administered for metastatic disease in 6 of them. 6 patients had prior hormonotherapy either in the adjuvant or metastatic setting. The sites of metastases were: bone (8), liver (6), pleura (5), lungs (4), brain (4), skin (3), nodes (3), bone marrow (2), choroid (1). The number of cures administered was 1 (n=2), 2 (n=1), 3 (n=1), 5 (n=3), 6 (n=4), 7 (n=2), 12 (n=1).

Results: The major toxicities were 2 cases of grade-4 neutropenia, one of which was associated with a septic shock resulting in death, and one case of grade-4 anemia. There were no cases of grade-3 or 4 digestive toxicities. 4 patients had grade-2 dysesthesia of the extremities and 1 patient had a cutaneous allergic reaction. There were no cases of alopecia > grade 1. 3 cases of complete remissions were obtained (hepatic, cerebral, pulmonary, and node metastases), 2 cases of partial remissions (pleuro-pulmonary and cutaneous metastases), and 5 cases of stability > or = to 3 months. 3 were non-responders and 1 patient is not yet evaluable and is currently undergoing treatment.

Conclusion: Even though our patient population was heavily pretreated for an evolved metastatic disease, this treatment combination results in an interesting number of responses, with minimal toxicity, and merits being studied further.

Updated results (time-related parameters) will be presented.

COMBINING GEMCITABINE (GEM) AND CAPECITABINE (CAP) IN ADVANCED PANCREATIC CANCER. RESULTS OF A PHASE I-II TRIAL.

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GEM is presently used as standard agent in advanced pancreatic cancer, although its advantage compared to 5-fluorouracil (FU) given as weekly bolus injection is small. Preclinical studies suggest positive interactions between GEM and CAP, an oral FU prodrug. In this study we investigated the addition of CAP to GEM in patients with advanced pancreatic cancer. Patients (pts) were required to have histologically or cytologically confirmed, inoperable or metastatic pancreatic cancer, no prior chemotherapy, KPS 60%, no significant concomitant disease, alkaline phosphatase < 5× and bilirubin < 1.5× upper normal limit. GEM was given at a fixed dose of 1 g/m² days 1+8. CAP was given orally twice daily for 14 days. Treatment was repeated every 3 weeks. Starting dose for CAP was 1000 mg/m²/d (level 1). Escalations were planned to 1300 mg/m²/d (level 2) and 1600 mg/m²/d (level 3). Maximum tolerated dose (MTD) was defined as the dose causing dose limiting toxicity (DLT) in 1/3 of a cohort of at least 6 patients. DLT has been defined as thrombocytopenia or neutropenia grade 4, febrile neutropenia, stomatitis or diarrhea 3, hand-foot-syndrome grade >3 according to NCIC CTC. 26 pts have been registered for the phase I part. DLTs have been documented in 1/9 pts in dose level 1, 1/11 pts in level 2 and 2/6 pts in level 3 resp. and consisted of myelotoxicity and stomatitis. Other toxicities have been mild and easy to manage. Hand-foot-syndrome and alopecia have not been observed. In addition 8 more pts have been treated in dose level 2 in order to gain more experience with this regimen. At this point 21 pts with measurable disease are evaluable for response. Of these 6 pts (28.6%) achieved a partial response. Responses have been observed on all three dose levels. In addition, there have been several dramatic CA 19-9 decreases and clinical benefit responses. This seems to be a highly active drug combination in pancreatic cancer. Dose level 2 will be tested in phase III.

STANDARD (SCT) VERSUS DOSE-INTENSIFIED CHEMOTHERAPY (ICT) WITH SEQUENTIAL RE-INFUSION OF PERIPHERAL BLOOD CELLS (PBC) IN SCLC

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Objective: The aim was to determine whether administering an increase in dose intensity of ICE chemotherapy is associated with an increase in survival at 2 years in pts with good prognosis SCLC.

Methods: Eligibility criteria included: Manchester Score (MC) 0–1; age <70 yrs, no prior tumor therapy, normal hematologic, renal, hepatic function, no brain metastases. Chemotherapy consisted of ifosfamide 5 g/m² d1 (24 h), carboplatin 300 mg/m² d1, etoposide 180 mg/m² d1+2. In pts on ICT, cycles were repeated.

q2w x6 and G-CSF (300–480 µg) was given d4 to d13. Whole blood (750 ml) was collected on d15 prior to ICT and re-infused on d3. In pts on SCT cycles were repeated every q4w x6.

Results: From 10/96 to 6/98 a total of 40 pts have been entered, (ICT n=20, SCT n=20). Median age was 53 years. 21 pts had MC 0, 19 pts MC1. Male/female ratio was 31/9. LD/ED ratio was 38/2. A total of 225 CT courses have been delivered (ICT: 124, SCT 101). The main toxicity was hematologic, however, there was no difference in hematologic and non-hematologic toxicity between ICT and SCT. 36 pts responded (CR/PR): 20 pts on ICT (9 CR/11 PR), and 16 pts on SCT (10 CR/6 PR). In pts on ICT, MS was 22.9 mo, in pts on SCT 17.8 mo. 1-year-SR and 2-year-SR was 85 and 50% pts on ICT and 85 and 25% on SCT.

Conclusion: ICE with whole blood -/ peripheral blood stem cell support is feasible and effective. Moreover, preliminary data indicate survival benefits for ICT over SCT. This randomized study therefore is ongoing in order to obtain confidence-intervals.