the average LNR distributions: low LNR⩽0.25, intermediate LNR more than 0.25 up to 0.75, and high LNR > 0.75. Survival analyses used the Kaplan-Meier method. End-point was death from any cause. Significance testing used the logrank. Chi-square values are reported for stomach and colorectal to allow comparison with the relevant TNM subdivisions.
Results: Median follow-up was 91 months. Five-year survival rates by site and by LNR were respectively:

Site	Nb. patients	Low-LNR	Mid-LNR	High-LNR	Logrank P
Esophagus	576	16%	5%	4%	<0.0001
Stomach	3381	31%	16%	7%	<0.0001
Small intestine	508	66%	52%	51%	0.035
Colorectal	26181	49%	30%	15%	<0.0001
Anal canal	102	39%	25%	22%	0.187
Hepatobiliary	346	21%	19%	7%	<0.0001
Pancreas	660	11%	9%	8%	0.029

Chi^2 based on relevant TNM subdivisions was 192.3 for stomach, and 1488.7 for colorectal. Respective Chi^2 based on LNR were 438.4 and 2723.0, indicating better prognostic separation with the LNR. As in Figure 1, other sites also showed better separation with LNR.
Conclusions: The lymph node ratio performed consistently in all digestive sites. Further investigations on its role for staging are warranted.

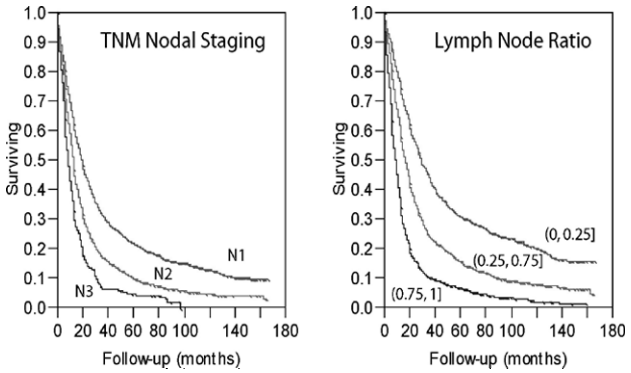

Figure 1. Survival in stomach carcinoma, as classified by the pN nodal staging (left), or by the Lymph node ratio (right). The separation between is notably better with the Lymph node ratio.

739 POSTER

Postoperative adjuvant chemotherapy in Japanese gastric cancer patients using Doxifluridine, an intermediate metabolite of Capecitabine, and 5-Fluorouracil – randomized controlled trial

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Objective: To investigate the usefulness of doxifluridine (5'-DFUR) in comparison with 5-Fluorouracil (5-FU) in postoperative adjuvant chemotherapy for gastric cancer including the association with levels of thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD).
Materials and methods: Patients with disease stage II, III-a, or III-b and curability of A or B gastric cancer were eligible for the study, and were randomized using minimization method (stratification factors: disease stage, curability, TP level, and gender), patients were allocated either to 5'-DFUR (400 mg/m^2) or to 5-FU (100 mg/m^2) group. After surgery, patients in each group were administered per orally doxifluridine or 5-fluorouracil daily for 2 years, and they were followed up post-operatively for 5 years. Based on the Kaplan-Meier method, a treatment-specific disease-free survival curves (DFS) and survival curves were estimated for comparison. As the secondary study, levels of DPD were also measured to compare doxifluridine and 5-fluorouracil by the TP/DPD ratio.
Result: During the period from September 1995 to August 1998, 212 patients were enrolled at a total of 48 medical institutions. There was no major bias between the two groups in demographic factors. In terms of a DFS curve and a survival curve in all patients at the post-operative 5-year time point, there was no statistical difference between the two groups. In a stratified log-rank test and a TP/DPD ratio-specific investigation as well, similar results to the above were obtained. DFS curves in patients with measurable DPD levels in the high- and low-TP/DPD-ratio groups were estimated. As a result, DFS curves in patients in the high-TP/DPD-ratio group were found to be significantly better (P = 0.043: log-rank test). This tendency was found to be more relevant in patients in the 5'-DFUR group.
Conclusion: In comparison of 5'-DFUR and 5-FU treatment in postoperative adjuvant chemotherapy for gastric cancer, no statistical difference was observed in either the DFS curve or survival curve. In the TP/DPD ratio-specific investigation conducted as the secondary study, patients with the high-TP/DPD-ratio group had significantly better DFS and survival curves, regardless of the treatment. Thus, the TP/DPD ratio was considered to be useful in predicting responses in the treatment using fluorinated pyrimidines, especially with 5'-DFUR.

740 POSTER

Fluorouracil, leucovorin and oxaliplatin (FLO) versus fluorouracil, leucovorin and cisplatin (FLP) as a first line therapy in patients with advanced gastric cancer –interim analysis of a multicenter, randomized phase II trial

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Background: Cisplatinum-based chemotherapy is widely used as first-line treatment for advanced gastric cancer which is, however, associated with limited efficacy and significant toxicities. The purpose of our study was to evaluate tolerability and efficacy of oxaliplatin combination chemotherapy in patients (pts) with advanced gastric cancer.
Methods: Patients were required to demonstrate adequate liver, renal, and haematological function and ECOG performance status 0–2 to participate. Participants were randomised to receive FLO: Fluorouracil (F) 2600 mg/m^2 24 h infusion, leucovorin (L) 200 mg/m^2, and oxaliplatin 85 mg/m^2 every two weeks or FLP: F 2000 mg/m^2 24 h infusion, L 200 mg/m^2, weekly, and cisplatin 50 mg/m^2 every two weeks. Primary end point was progression free survival. To evaluate safety and response a planned interim analysis was performed after 80 patients had been randomized and completed at least one treatment cycle.

	FLO n = 44		FLP n = 36	
Safety (NCI)	All grades	Grades 3/4	All grades	Grades 3/4
Vomiting (%)	29.5	4.5	44.4	2.8
Diarrhea (%)	25	0	22.2	2.8
Stomatitis (%)	13.6	0	11.1	2.8
Infection (%)	4.5	0	8.3	2.8
Neurosensory (%)	54.5	9.1	19.4	0
Anemia (%)	45.5	0	55.6	2.8
Leucopenia	31.8	0	33.3	11.1
Thrombopenia	31.8	9.1	19.4	0
Response (WHO)*	**n/41**	**%**	**n/33**	**%**
CR	2	4.9	0	–
PR	14	34.1	8	24.2
SD	19	46.3	15	45.5
PD	6	14.6	10	30.3

*p = 0.072

Results: 140 pts have been randomized so far. Results for toxicity and response on the first 80 pts are shown in the table. Progression free survival was 5.6 months (FLO) vs. 3.6 months (FLP) (p = 0.90).

Conclusions: The oxaliplatin combination chemotherapy showed promising activity. The overall toxicity was low in both arms, therefore no dose adjustments were performed. Based on these results it was recommended to extend the study (as planed per protocol) into a phase III trial with a planned accrual of 216 pts.

741 POSTER

Capecitabine-oxaliplatin (XELOX) in hepatocellular carcinoma (HCC): preliminary results of a multicentric phase II study (FFCD 0303)

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Background: There is no standard systemic chemotherapy for patients with advanced HCC. Evaluation of new drug combination is needed in this poor prognosis disease. The trial was designed to evaluate the efficacy of XELOX in HCC.
Material and methods: Inclusion criteria: patients with measurable HCC non suitable for surgery or percutaneous ablation; Child-Pugh A or B, CLIP <4. Every 3 weeks patients (pts) received: capecitabine 2000 mg/m^2 d1-d14, oxalipaltine 130 mg/m^2 d1. The main endpoint was tumor response.
Results: From December 2003 to September 2004, 50 pts were included in this phase II trial: 44 men, 6 women; median age (range) 68 years [24–82]; PS (OMS) 0/1/2: 22/25/3 patients; Child-Pugh score A, 42 pts and B, 8 pts; CLIP 0–1, 21 pts, CLIP 3–4, 29 pts. The median number of cycles was 6 [1 – 14]. Grade 3–4 toxicity: neutropenia: 2 pts, febrile neutropenia 1 pts, thrombopenia: 5 pts; diarrhea 8 pts, nausea/vomiting: 2 pts, mucitis, 1 pts; hand foot syndrome: 2; cardiovascular 2 pts. Grade 2 and 3 neuropathy was observed in 9 and 3 pts. There were two toxic deaths: one myocardial infarction and one neutropenic infection. Overall response (39 evaluable pts): partial response (3 pts), stable disease (29 pts). The intent to treat disease control rate (RP + SD) = 64% (IC 95% = 49–77%). Median PFS and OS were 4.8 and 9.3 months, respectively.
Conclusion: Capecitabine and oxaliplatine combination is feasible in patients with HCC and compensated cirrhosis. Despite a low response rate, this regimen provides an interesting disease control rate (64%) and overall survival (9.3 months) with manageable toxicity in non pre-treated advanced HCC patients.

742 POSTER

A prospective multicenter phase II trial of capecitabine plus oxaliplatin (CAPOX) in advanced biliary system adenocarcinomas

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Objective: To evaluate the safety and efficacy of capecitabine and oxaliplatin combination therapy (CapOx) in unresectable or metastatic adenocarcinomas of the biliary system.
Methods: 62 pts (26M, 36F) were enrolled (median age, 63 yrs). Major eligibility: histologic proven, measurable disease, age $\leqslant$75 yrs, ECOG PS $\leqslant$2. A total number of 331 cycles (median: 5; range 1–16) of oxaliplatin (130 mg/m^2, d1) plus capecitabine (2000 mg/m^2, d 1–14) were administered 3 weekly for gallbladder carcinoma (GBC) (25 pts), extrahepatic (20 pts), and intrahepatic (17 pts) cholangiocarcinoma (CCC). Response rates were assessed according to WHO standard criteria. Clinical outcome was determined separately for pts with either GBC/extrahepatic CCC or intrahepatic CCC (mass-forming type).
Results: Grade 4 toxicities (WHO) were diarrhea in 1 pt (1% of cycles), thrombocytopenia in 1 pt (1%), leukopenia in 1 pt (1%), and fever in 2 pts (1%); grade 3 toxicities were nausea/vomiting in 1 pt (1%), diarrhea in 2 pts (1%), thrombocytopenia in 3 pts (2%), and fever in 1 pt (1%). Grade 3/4 peripheral sensory neuropathy (Lévis scale) was found in 13 pts (14%). Two pts were removed from study because of oxaliplatin-related allergic reactions. One patient died due to sepsis and another due to cerebral insult after the first treatment cycle, respectively. The overall disease control rate on 42 evaluable pts with GBC or extrahepatic CCC was 69% (complete response (CR), n = 2 (5%); partial response (PR), n = 8 (19%); stable disease (NC), n = 19 (45%)), whereas progressive disease (PD) was found in 13 pts (31%). In 17 evaluable pts with intrahepatic mass-forming CCC, we observed no CR or PR, but 5 pts (29%) had SD, and in 12 pts (71%) PD was encountered.
Conclusions: The CapOx protocol appears to be well tolerable and highly active for advanced GBC and extrahepatic CCC (disease-control rate: 69%), whereas clinical results might be poorer in the subset of intrahepatic mass-forming type tumors. Survival data will be presented at the meeting.

743 POSTER

Second primaries in patients with gastric cancer: clinical significance and treatment outcome

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Background: We investigated (1) whether second primaries affect the treatment strategy and outcome of gastric cancer and (2) whether neoadjuvant radiation therapy in moderate doses increases the incidence of metachronous tumors.
Material and methods: Between 1974 and 2003, 941 patients with gastric cancer underwent curative surgery and were the subjects of the study. In 377 patients surgical treatment was used while in 564 patients it was combined with adjuvant radiotherapy. Intensive preoperative regimens (20–27 Gy/5–11 days) were used in 495 patients. In 69 patients both preoperative and intraoperative radiation therapy (IORT, 20 Gy) were used.
Results: Second primary tumors with extragastric location were observed in 62 (6.6%) patients including 22 cases diagnosed and treated before gastric surgery (median interval 11.5 years); 23 cases of synchronous tumors and 20 cases diagnosed and treated after gastric surgery (median interval 8 years). Among second malignancies colorectal cancer predominated (14 cases). Groups of patients with and without second primaries did not differ significantly concerning most prognostic factors except for T-stage ($p = 0.0004$). Curative treatment for the second tumor was performed in 53 (82%) patients, the most frequent treatment modality was surgery alone (23 cases) followed by multimodal (16) and radiotherapy (13). 5- and 10-year survival rates in patients with and without second primaries did not differ significantly ($p = 0.13$). A significant difference was seen in the cause of patients' death depending on the time of the second tumor appearance. When they were treated before gastric cancer none of them resulted in patients' death. In the case of synchronous tumors they were the cause of death in the half of the patients. Metachronous tumors were responsible for the patients' death in all the cases (12). In surgical group metachronous malignancies developed in 9 (2.4%) patients; in radiation therapy group – in 11 (1.9%) patients including 1 (1.5%) patient in IORT group.
Conclusions: Second primaries are seen in 6.6% of patients with gastric cancer and in 12.5% of patients with early gastric cancer. Second tumors are not the contraindication for the curative treatment of each of the lesions but they do significantly affect the prognosis of the treatment. Moderate doses of preoperative radiotherapy and its combination with IORT do not increase the incidence of metachronous tumors after curative surgery for gastric cancer.

744 POSTER

Hepatic arterial infusion of carboplatin mixed with degradable starch microspheres by using implanted reservoir in patients with advanced hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is common cancer worldwide. Because HCCs are chemotherapy-resistant tumors, and current systemic therapy has been unable to prolong survival, hepatic arterial infusion chemotherapy is usually used for the treatment of multifocal bilobar tumors of the liver, not amenable to transcatheter arterial chemoembolization (TACE). The purpose of this study (a phase II study) was to determine the efficacy and toxicity of carboplatin mixed with degradable starch microsheres (DSM) in patients with HCCs and underlying cirrhosis.
Methods: Patients with histologically confirmed advanced HCCs not amenable to surgery, PEI (percutaneous ethanol injection) and TACE were eligible for the study. Other eligibility criteria included an age of 20 to 75 years; a stage of 4-A; adequate hematological, renal and liver function; and informed consent. All patients had associated liver cirrhosis, and were implanted an infusion catheter connected with a reservoir to the hepatic artery via the femoral artery by percutaneous method. Carboplatin (175 mg/m^2) mixed with DSM (175 mg/m^2) and Lipiodol (<3 ml) was administered as a single bolus injection from the hepatic artery through