group. Median survival is 27 months. Six months and 1 year survival is 89% and 71% respectively. Stage related 3 year actuarial survival was for stage I: 91%, stage II: 50%, stage III: 53% and stage IV: 20%. Late mortality was cancer related in 41 patients: distant metastasis: 23, distant metastasis + locoregional recurrence: 10, locoregional recurrence: 8. Quality of survival of the 55 survivors showed an excellent or good feeding capacity in 49 (89%) patients. Nine patients developed an anastomotic stricture treated with a mean of two dilatations. Weight status showed a mean decrease of −7.3 kg (−33 kg to +10 kg) as compared to the preoperative weight and −3. kg (−26 kg to 17 kg) as compared to the patients ideal weight. Final Visick score was grade I: 34 (61%), II: 11 (20%), III: 7 (12%), IV: 3 (5.4%). *Conclusion:* Today oesophagectomy for carcinoma can be performed with a minimum mortality and acceptable morbidity. Risk factors have to be judged individually especially in relation to radicality of associated lymphadenectomies. Survival is as expected stage related but even in distant lymphnode metastasis acceptable prolonged palliation is obtained with excellent to very good functional outcome in the majority of patients justifying resection or primary treatment in absence of gross tumour spread or solid organ metastasis.

543 ORAL

THE ROLE OF INTRA LUMINAL BRACHYTHERAPY IN TREATMENT OF CANCER OF THE OESOPHAGUS

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A prospective, non-randomized study was performed in 201 patients with inoperable cancer of the oesophagus. 101 were treated with palliative reason with Intra Luminal Brachytherapy (ILB), (n = 56), or combined External Beam RadioTherapy (EBRT) and ILB, (n = 45). 100 patients were treated with Radical Radiotherapy: group 1) 50 Gy EBRT + 2 × 7.5 Gy ILB, (n = 54), group 2) 60 Gy EBRT + 2 × 6 Gy ILB, (n = 46).

Results: ILB as single modality treatment results in good, life long improvement of dysphagia. Median survival is 3.4 months and 1-year overall survival 5%. EBRT + ILB has equal effects, with median and 1-year overall survival of 4.7 months and 13% respectively.

Treatment related complications were rare. In the radical group 50 Gy + 2 × 7.5 leads to a median, 1- and 2-year survival of 9.3 months, 40% and 13% respectively. For 60 Gy + 2 × 6 this was 11.8 months, 43% and 31%. Complications were mild.

Conclusions: Intraluminal Brachytherapy is save and effective in palliation for carcinoma of the oesophagus. Results with intraluminal brachytherapy alone are comparable with combination of EBRT + ILB. In Radical Radiotherapy increasing EBRT dose from 50 to 60 Gy + ILB 2 × 6 Gy increases local control as well as overall survival.

544 ORAL

ECF IS A HIGHLY ACTIVE REGIMEN WITH LOW TOXICITY SUITABLE FOR NEOADJUVANT TREATMENT OF OESOPHAGOGASTRIC CANCER

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Initial trials with ECF demonstrated a 71% response in oesophagogastric cancer with modest toxicity, renewing interest in neoadjuvant therapy. We now report our experience of 235 consecutive patients treated between 1989 and 1994. All diagnoses were histologically proven. The regimen comprises epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 3 weekly × 6–8 with protracted venous infusion 5-FU 200 mg/m^2/d throughout. Responses were evaluated with CT scan and gastroscopy. 173 patients had metastatic disease and 62 had locally advanced disease (LAD). Measurable response occurred in 135/220 (61%, 95% CI 55–68%) with CR in 11% and PR in 50%. Symptomatic response occurred in 50–85%. Quality of life was improved or maintained in most patients. Toxicity was modest; 22% grade 3/4 leucopenia and 14% grade 3/4 non-haematological toxicity. There were 6 treatment related deaths, all during the first 3 years. 29 patients with LAD who responded proceeded to surgery. 19 (66%) had a potentially curative resection; histological CR was demonstrated in 6 (32%). Overall median survival was 256 days. Patients with LAD and ECOG performance status 0–2 had a median survival of 404 days with a 1 year failure free rate of 40%. We conclude ECF is a highly active regimen with acceptable toxicity that can render locally advanced tumours operable. This potential is being evaluated in the MRC "MAGIC" trial comparing ECF before surgery with surgery alone.

545 ORAL

SECOND MALIGNANCIES (SM) IN ESOPHAGEAL CANCER (EC) AFTER COMBINED MODALITY TREATMENT: IMPLICATIONS FOR FOLLOW-UP AND CHEMOPREVENTION

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From 5/85 to 12/92, 101 consecutive patients (median age: 61 yrs), with locally advanced EC received a combined chemoradiotherapy treatment, Sixty-one pts were treated with FU + CDDP × 4 cycles and concurrent RT (50 Gy) and 40 pts with 2 courses of the same regimen plus concurrent RT (30 Gy) followed by surgery. Overall survival (OS) at 6 yrs was 22%. In 14 pts EC developed after a previous neoplasm and they were excluded from the analysis. In the remaining 87 pts with primary EC (OS 23% with a median follow up of 77 mos) a total of 12 pts (median age 67 yrs, range 49–79) developed a SM after a median of 27.5 mos (range 7–83) from the diagnosis of EC: 4 epidermoid head and neck cancers, 3 gastric adenocarcinomas (1 early gastric cancer), 1 distal esophageal adenocarcinoma, 2 non small cell lung cancers, 1 colon adenocarcinoma, and 1 vaginal squamous cell carcinoma. Actuarial cumulative risk for SM at 2, 4, and 6 yrs is 6%, 17%, and 23% respectively. Total incidence rate was 6% with an age-adjusted incidence of SM 3 times higher than that of primary cancer in the general population. The high incidence of SM in long-term survivors with EC strongly supports a prolonged follow-up oriented to the early detection of SM. This population with high rate of SM should represent an optimal model to assess the role of chemoprevention.

546 ORAL

ADVANCED GASTRIC CANCER: COMPARISON OF FAMTX (5FU, ADRIAMYCINE, METHOTREXATE) VERSUS ELF (ETROPOSIDE, 5 FU, LEUCOVORIN) VERSUS FUP (INFUSIONAL 5 FU + CISPLATIN). RESULTS FROM AN EORTC TRIAL OF THE GITCCG AND THE ARBEITSGEMEINSCHAFT FÜR INNERE ONKOLOGIE (AIO)

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FAMTX, shown superior to FAM (*J Clin Oncol* 1991;9:827) has been compared to ELF (*Sem Oncoll* supp2, 1990) and FUP (*Eur J Cancer* 1994;**30A**:1263). Eligibility criteria included locally advanced and/or metastatic gastric cancer, measurable, evaluable or non measurable disease, performance status O-2, age < 76 years and adequate organ functions. A total of 373 pts were randomized by 52 institutions. This preliminary analysis is based on 274 eligible pts. Grade 3–4 toxicities were (ELF-FUP-FAMTX): vomiting 8-25-10%; mucositis 3-13-10%; leucopenia 6-4-7%; thrombocytopenia 0-4-2%. There were 5 toxic deaths (2 FUP and 3 FAMTX). The median number of cycles was 4 (1–8), 4 (0–6) and 3 (0–6) respectively. Extramurally reviewed objective response (OR) in 132 assessable pts with measurable disease was; ELF 21%; FUP 27%; FAMTX 20%. SD was achieved in 35%, 41% and 42% respectively. Downstaging with subsequent resection was achieved in 0/15, 2/18 and 4/16 respectively. Median survival was 7, 8, 7 mths respectively. *In conclusion* no significant differences in response or survival were detected. The low OR rate may be due to the number of pts receiving no (3%) or only one cycle of chemotherapy (12%, 14% and 20% respectively) and to the number of institution which entered less than 4 pts (n = 19).

547 ORAL

IMPROVEMENTS IN SURVIVAL AND CLINICAL BENEFIT WITH THE USE OF GEMCITABINE (GEM) AS FIRST-LINE THERAPY FOR ADVANCED PANCREATIC CANCER: A RANDOMIZED TRIAL

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Following phase II clinical observations that patients with pancreas cancer experienced improvement in disease-related symptoms with GEM, a quantitative definition of clinical benefit (CB) was developed as a primary efficacy measure (Andersen, 1994, *Proc ASCO* 13:461). CB has

3 components: pain (based on analgesic consumption and pain intensity), Karnofsky performance status, and lean body mass increase. Each parameter was measured at baseline and regularly during study. Clinical benefit was define as a sustained improvement (≥4 weeks) in at least one parameter without a worsening in any other. Following a lead-in period to characterize and stabilize pain, 126 chemonaive patients with confirmed advanced or metastatic adenocarcinoma of the pancreas (measurable or evaluable) were randomized to GEM 1000 mg/m^2 over 30 min wkly × 7 followed by 1 wk of rest, and then wkly × 3 every 4 wks thereafter, or to 5FU 600 mg/m^2 over 30 mins once wkly. Patients on both treatment arms were balanced in terms of gender, age and disease stage. CB response was the primary endpoint: 23.8% of the GEM pts were CB responders versus 4.8% of 5FU pts ($P = 0.0022$). The median survival (months) was 5.65 for GEM versus 4.41 for 5FU ($P = 0.0025$), with 24% of GEM pts and 6% of 5FU pts alive at 9 months. WHO ≥ grade 3 neutropenia was seen in 23% of GEM pts and 5% of 5FU pts, and ≥ grade 3 non-hematological toxicity (N&V, diarrhea) was seen in 15% of GEM pts and 10% of 5FU pts. This randomized study confirms the previously reported positive effect of gemcitabine on clinical benefit, and shows a survival benefit for GEM as initial treatment of patients with pancreatic cancer.

548 ORAL

PET FOR VISUALIZATION OF C-11-L-DOPA UPTAKE AND DECARBOXYLATION IN ENDOCRINE PANCREAS CANCER

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In the old classification system endocrine pancreas tumors were described as APUDomas. This property of neuroendocrine tumors, to take up amine precursors for decarboxylation to monoamines, has been used for the diagnosis *in vivo* with positron emission tomography (PET). C-11-labelled DOPA is administered to the patients and a very high accumulation of radioactivity facilitates its identification. In two patients succeeding studies were performed with L-DOPA labelled alternatively in the β-position and in the carboxyl-group. When labelled in the β-position, the radioactivity follows the molecule to dopamine and hence a high accumulation is observed. When labelled in the carboxyl-group, the radioactivity is cleaved off as carbon-dioxide and eliminated from the tissue. This results in a low uptake in the tumor. With analysis of the kinetics, the rate of decarboxylation in the tumors is calculated.

In the same patients, examinations were performed before and after the treatment with somatostatin analogue. After treatment a 2-fold increase in the tracer accumulation is observed. This finding is explained as an indication that somatostatin analogues have minor effects on the uptake and decarboxylation process but a significant effect on release of monoamines.

549 ORAL

CAUSES OF DEATH AND RISK OF SECONDARY MALIGNANT TUMOURS IN PATIENTS WITH MALIGNANT TUMOURS OF THE SMALL BOWEL

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Background: There are few systematic studies of co-morbidity and risk of other cancers in patients with malignant tumours of the small bowel.

Methods: We studied 926 cases with adeno carcinoma of the small bowel and 1661 cases of carcinoid tumours reported to the Swedish Cancer Registry 1966 through 1988. Follow-up was available until 1990. The misclassification for both diagnoses was less than 5%. Standard mortality ratio (SMR) and standard incidence ratio (SIR) for second tumours were calculated.

Results: The patients with *adeno carcinoma* had increased risk to die from malignant diseases (tumours of the small bowel excluded, SMR 12.8), hematological and gastrointestinal diseases. They also had increased risk of acquiring a cancer in the female genital organs and in the gastrointestinal tract (SIR 3.5). Patients with *carcinoid tumour* showed increased risk of a tumour in the male genital organs (SIR 1.9). Standard mortality ratio was increased for endocrine disease (SMR 36.0), for cardiovascular and for gastrointestinal disease. The SMR for dying from another malignancy was 6.2).

Conclusions: Our findings support an earlier hypothesis about an association between carcinoid tumours and prostate cancer. The novel findings of associations between adeno carcinomas and risk of death in hematological disease and of carcinoid tumours and risk of dying from other, non-neoplastic endocrine disorders are relevant for further clinical investigations.

550 POSTER

GEMCITABINE IS EFFECTIVE AS PALLIATIVE THERAPY FOR 5FU-REFRACTORY PANCREAS CANCER PATIENTS

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In a previous phase II trial of gemcitabine in pancreas cancer, numerous patients experienced a reduction in cancer-related symptoms and improvement in performance status. Since pancreas cancer is highly symptomatic, and therapy is difficult to assess using traditional endpoints, we designed and conducted a prospective, multicentre phase II trial with clinical benefit as the primary endpoint. Clinical benefit response was defined as a ≥50% reduction in pain (measured on a visual analogue scale), a ≥50% reduction in daily analgesic consumption, or a ≥20 point improvement in Kamofsky performance score (KPS), that was sustained for ≥4 weeks without worsening in any other component. Gemcitabine 1000 mg/m^2 (30 min infusion) was administered q wk × 7 followed by 1 wk rest, and thereafter in cycles q wk × 3 followed by a 1 wk rest. 63 pts (32 M, 31 F) with pancreatic adenocarcinoma that had progressed despite 1 prior 5-FU-based therapy were enrolled. Median age: 62 (range 33–77). Median KPS: 70 (range 50–90), median baseline pain intensity: 29 on a 100 point scale (range 3–68), median baseline analgesic requirement: 60 mg morphine-equivalents/day (range 0–1159). Therapy was very well tolerated with grade 4 toxicities reported for nausea, vomiting, neutropenia, bleeding or anaemia (each in 1 pt, 2%). Grade 3 toxicities included neutropenia (25% pts), anaemia (10%), thrombocytopenia (5%), and nausea/vomiting (6%). Under these stringent criteria, 17 of 63 pts (27%) attained a clinical benefit response (95% CI: 16–38%). We conclude that objective criteria can be used to evaluate new therapies for pancreas cancer, and that gemcitabine has substantial activity as a palliative agent.

551 POSTER

HIGH DOSE RADIOTHERAPY (RT), CONCOMITANT CHEMOTHERAPY (CT) AND HIGH DOSE RATE BRACHYTHERAPY FOR NON RESECTABLE ESOPHAGEAL CANCER

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RT and concomitant CT is the standard treatment for non resectable esophageal cancer. Usual total radiation dose is 50 Gy. In order to enhance local control rate a phase II study was initiated to evaluate the feasibility of a combined treatment with an external radiation dose of 60 Gy and 3 cycles of concomitant CT followed by a high dose rate brachytherapy delivering 10 Gy (2 applications with 7 days interval). 73 patients (pts), 28 men and 5 women were treated between 1989 and 1993. Stages were evaluated with CT scan and with endoscope sonography for 41 pts: 13 were Stage IIB, 50 Stage III and 10 Stage IV. Treatment consisted in a conventional fractionated RT to a total dose of 60 Gy delivered with 2 Gy per fraction, one fraction per day and 5 fractions a week. The CT regimen was a combination of Cisplatinum 25 mg/m^2 d1 to d4, 5 Fluorouracil 600 mg/m^2 continuous infusion d1 to d4. 3 cycles were administered on d1, d22 and d43. Brachytherapy was delivered one week after the end of external radiation therapy. Full radiation therapy dose was delivered for 96% of the patients. CT compliance, evaluated on the drug dose and the CT interval, was good for 77% of the patients. Overall grade 3 and 4 WHO toxicity rates were 23% and 7% respectively. One pt died from treatment toxicity. Local control rate at one year was 74%. Three-year actuarial survival rate was 27%. Distant metastase was the main cause of treatment failure. Predictive factors of late effects related to brachytherapy and evaluation of a swallowing score will be presented, In a multivariate analysis Stage was the only prognostic factor. In conclusion this regimen with high dose RT and 3 cycles of concomitant CT is feasible. Treatment results are very encouraging for pts with locally advanced disease.