**Conclusions:** The combination of CPT-11 with gemcitabine is an active and well tolerated regimen in the treatment of metastatic breast cancer patients pretreated with taxanes and anthracyclines.

723 POSTER

### 'Faslodex' (ICI 182,780) 250 mg shows consistent pharmacokinetic profile when given as either a one x 5-ml intra-muscular (i.m) injection or two x 2.5-ml injections in postmenopausal (PM) women with advanced breast cancer (ABC)

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Faslodex (ICI 182,780)(FAS), is a novel estrogen receptor downregulator that has no estrogen agonist activity. FAS is administered as 250 mg i.m injection once monthly. In the North American based FAS trials, differences in clinical practice preferences led to FAS 250 mg being given as 2 x 2.5 ml injections as opposed to 1 x 5 ml dose in Europe/Rest of World based trials. Given the differences in dose administration within the FAS breast cancer trial programme, it was therefore considered important to compare the PK of FAS when given as either 1 x 5 ml dose or 2 x 2.5 ml dose.

Here we report the PK findings of an open, randomized multicentre, parallel-group trial in PM women with ABC. Patients (n=38) were randomly assigned to either a single dose of FAS, as 1 x 5-ml injection (n = 20) or 2 x 2.5-ml injections (n = 18). Blood samples for PK analysis were taken at various time points up to 28 days after treatment. Tolerability assessments were also made. PK parameters included AUC0-28days, C28 days, Cmax and tmax. Safety follow-up continued until 8 weeks after the injection was given.

The geometric mean AUC0-28days blood levels were 106.8 ng.day.ml and 105.5 ng.day.ml for 1 x 5 ml and 2 x 2.5 ml respectively. The ratio of the geometric means of 1.01 (95% CI 0.68*1.51) showed there was no significant difference in AUC between the two dose regimens (p=0.94). The geometric means of C28 days, and Cmax and the median of tmax were similar in both treatment groups. Both treatment regimens were well tolerated, with there being no major differences in adverse events. The data from this study were in line with AUC0-28 days data from an earlier study involving postmenopausal women with primary breast cancer, where based on 22 women receiving FAS 250 mg (1 x 5 ml), the geometric mean AUC0-28 day was 116.5 ng.day.ml.

In conclusion, there was no significant difference in PK and adverse events between 1 x 5-ml injection and 2 x 2.5-ml injections of FAS. Based on these PK findings, the dosing regimen employed with FAS in the clinical setting would not be expected to impact on the clinical outcome indicating that the 250 mg dose of FAS may be administered as either 1 x 5-ml injection or 2 x 2.5-ml injections. Additionally the single-dose PK findings in two trials using FAS 250 mg (1 x 5 ml) demonstrate the consistency of FAS PK between trials.

724 POSTER

### Cardiac safety of herceptin(R) in combination with epirubicin plus cyclophosphamide: interim results of a phase II study in patients with metastatic breast cancer

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The monoclonal antibody Herceptin" (H) is indicated for treatment of HER2-positive metastatic breast cancer (MBC), as monotherapy or in combination with Taxol. Previous trials have shown that the concomitant use of an anthracycline (A)-containing regimen (doxorubicin (D)) plus cyclophosphamide (C)) together with H is associated with an increased risk of cardiotoxicity as compared to DC alone. Epirubicin (E) is considered to have less cardiotoxic potential than D. This phase II study was designed to compare the incidence of cardiotoxic events in patients treated with EC plus H, versus patients treated with EC alone. Dose-limiting cardiotoxicity was defined as (a) a decrease of left ventricular ejection fraction (LVEF) of more than 10% points from the screening value and below 50%, or (b) acute coronary syndrome including MI, cardiopulmonary resuscitation, congestive heart failure or severe rhythm disturbances. Patients with HER2-positive disease would all receive EC+H. A control arm of HER2-negative patients would receive EC alone. The dose of E for the first 25 HER2-positive patients was 60mg/m2. Providing dose-limiting cardiotoxicity was not encountered, after completing 6 cycles of ECH, the dose of E would be escalated to 90mg/m2 for a second cohort. Subsequently, the number of patients in both active and control arms would increase to 100. All patients would have prospective cardiac monitoring using echocardiography and results would be reviewed by an independent cardiac review board.

Here we report the results of cardiac assessments in the first cohort of HER2-positive patients treated with 60 mg/m2 E, dose of C plus H (2mg/kg/week maintenance). Data are available for 25 patients. Baseline values for LVEF were in the range 57 to 82%. Four patients discontinued before reaching the sixth cycle of ECH for non-cardiac reasons. Five patients experienced non-serious cardiac disorders which did not coincide with changes in LVEF. An asymptomatic decrease of LVEF of more than 5% points was observed in 12 patients and 5 patients had an increase of more than 5% points. 8 patients experienced asymptomatic decreases of more than 10% points, and for 5 patients the decrease was transient. No dose-limiting cardiotoxic event was observed and LVEF values did not fall below 50% in any patient. Therefore, the Steering Committee has recommended dose escalation to 90mg/m2 E.

## Radiotherapy and radiobiology

725 POSTER

### Activity-Based Costing in radiotherapy: the costs of activities

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**Purpose:** to analyse the costs of the different activities within the Leuven radiotherapy process.

**Materials and methods:** an Activity-Based Costing model was developed for the calculation of radiotherapy costs in the Leuven radiotherapy department. Resource costs (wage, equipment, space, material and overhead costs) were collected for the year 1999, as well as data on that year's productivity. The resource costs were allocated to the final radiotherapy products based on the activity consumption necessary to produce the products. The activities of the radiotherapy department were defined as 30 treatment related activities and as care related and non-care related support activities. For this overview the treatment related activities were aggregated into 11 major activities and 4 activity groups (administration, treatment preparation and delivery and quality control).

**Results:** In 1999 the global resource costs of treatment related activities of the Leuven radiotherapy department amounted to 3.253.986 Euro. Wage, equipment, space, material and overhead costs accounted for respectively 45%, 25%, 23%, 4% and 3% of these global costs. The costs incurred by the different activity groups were 210 240 Euro, 1 008 625 Euro, 1 751 580 Euro and 283 540 Euro for administration, treatment preparation, treatment delivery and quality control respectively. Within treatment preparation simulation and planning roughly consumed the same amount of resource costs; i.e. 364 560 Euro and 324 760 Euro.

**Conclusion:** Wage and equipment consume a large proportion of the treatment related radiotherapy costs. Activities within the radiotherapy process that intensively employ staff and equipment are therefore most expensive, as has been shown in our data where radiotherapy delivery, simulation and planning turn out to be the three biggest resource consumers in radiotherapy. Treatment delivery is by nature a repetitive process, which explains that its costs by far outweigh the costs of other activities, even of the very complex ones, provided they only occur once or twice within the radiotherapy process.

726 POSTER

### Radiotherapy compared to extracorporeal shockwave therapy for supraspinatus tendinitis - randomised prospective single-blind trial with two-sample parallel group design

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**Aim:** In the case of supraspinatus tendinitis conservative therapy delivering either antiinflammatoric drugs or low-dose irradiation is the treatment of

choice. A novel approach is the using of Extracorporeal Shock Wave Therapy (ESWT) if the established treatment schedules have failed. So far there has been no controlled study comparing the effectiveness of ESWT with an established conservative therapy such as X-ray stimulation irradiation.

**Method:** Thirty patients with chronic supraspinatus tendinitis were admitted into this prospective randomised study. After randomisation the patients were treated either with low dose radiotherapy or with ESWT. Irradiation was performed using a cobalt 60 unit. The applied was 6 times 0.5 Gy and was delivered to the ICRU reference point (1 fraction/day) with cobalt 60 gamma rays. ESWT treatment occurred three times with 2000 pulses per session (energy flux density ED+ 0.1mJ/mm2) in one week intervals using a Storz Minilith SL1. Primary endpoint was the age-corrected constant score.

**Results:** In the radiotherapy group average the age-corrected constant score improved from 38.6 before radiotherapy through 63.9 points after 12 weeks to 70.4 points after 52 weeks. In the ESWT group it rose from 41.5 points to 76.4 points and 81.9 points, respectively.

**Conclusion:** No statistically significant differences were proven between radiotherapy and ESWT. ESWT appears to be equivalent but not superior to radiotherapy in treating chronic supraspinatus tendinitis syndrome. A comprehensive randomised study is however necessary to ensure the equivalence of ESWT.

727 POSTER

## Radiotherapy for age-related macula disease: a longitudinal single-arm study

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**Purpose:** To study the benefit from low dose fractionated radiotherapy in age-related macula disease (ARMD).

**Methods:** From 1997 to 1998, 72 patients with ARMD were enrolled. Patients with advanced cataract or concurrent retinal disease were excluded. 8 x 2Gy were administered to one eye in each patient. Fluorescein angiography and measurements of visual acuity were performed prior to, 3 mo., 6 mo., and 12 months after therapy. From 69 patients (30 classic ARMD, 39 occult ARMD) complete follow up data of at least 1 year were accessible to evaluation. The Wilcoxon rank test adjusted to serial tests (Bonferoni-Holm-method) was used to establish statistical significance. Acute and chronic potential side effects were also registered.

**Results:** The visual acuity decreased during follow up in 43/69, was stable in 18, and improved in 8 cases. The mean visual acuity deteriorated significantly (p=0.02). This holds true of both subtypes of ARMD. The most pronounced decrease of visual acuity occurred within the first 3 weeks. Occult ARMD did significantly better than classic ARMD (p=0.03). Neither age (p=0.17) nor sex (p=0.2) significantly influenced prognosis. 4 patients reported transitional complaints. Opacifaction of the ocular lens was not observed.

**Conclusion:** Low dose fractionated radiotherapy with 16 Gy is well tolerated. However, visual acuity is not preserved in the majority of ARMD patients. Despite promising initial reports our disappointing findings are in accordance with an increasing number of negative randomized and non-randomized published trials.

728 POSTER

## Hyperbaric oxygen does not enhance tumour growth and metastatic potential of the rhabdomyosarcoma R1H

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**Purpose/Objective:** There is concern that hyperbaric oxygen therapy might have cancer-enhancing properties. This analysis was performed to investigate whether hyperbaric oxygen affects tumour growth and influences metastatic potential in an experimental tumour system.

**Material and Methods:** WAG/Rij rats bearing the R1H rhabdomyosarcoma on the right flank were locally irradiated with 250 kV X-rays. The radiation dose ranged between 50-90Gy given in 22-30 fractions in an overall treatment time of six weeks. For radiation enhancement, animals inhaled room air under ambient conditions (n=38), or normobaric carbogen (95% O2; 5% CO2) (n=41), or hyperbaric oxygen at a pressure of 240kPa (n=41). The number of carbogen or oxygen exposures ranged between 2-30 (median: 6), and the oxygen exposure times were at least 10 minutes at treatment pressure. Animals were followed up to 150 days after the start of treatment. The incidence of local recurrence or metastatic lung disease was scored. Pulmonary metastases were verified by post mortem lung dissection. The time interval between tumour transplantation and first signs of lung metastases was analysed using Kaplan-Meier-statistics.

**Results:** Fourteen animals in air, 13 in carbogen and 10 in hyperbaric oxygen developed lung metastases. The median time interval for the occurrence of pulmonary metastases was 127 days (95%-CI: 101-153 days), 132 days (95%-CI: 116-148 days) and 137 days (95%-CI: 120-154 days) for air, carbogen and hyperbaric oxygen, respectively. In the Kaplan-Meier-analysis there were no differences between the three groups (log-rank-test>0.5).

**Conclusion:** Our data give no evidence that tumour growth and metastatic potential of the R1H rhabdomyosarcoma is enhanced by hyperbaric oxygen breathing.

729 POSTER

## The role of postoperative radiotherapy in the management of merkel cell carcinoma

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**Purpose:** Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine tumor of the skin with a high potential of locoregional relapse after surgery alone. The value of radiotherapy (RT) for curative treatment strategies was evaluated.

**Methods:** From 1/1990 to 5/2000, 31 patients with MCC (13 men, 18 women, age 34 - 92 years) were treated at the University of Cologne, Germany. Primary tumor sites were: head and neck region 13 pts., limbs 13 pts., trunk 5 pts.. The tumors were stage I (primary tumor alone) in 26/31 pts., stage II (locoregional metastases) in 4/31 and stage III (distant metastases) in 1/31. Treatment consisted of surgery alone in 14/31 pts., adjuvant postoperative RT in 16/31 pts. (one with incomplete surgery), and definitive RT in 1 patient with a stage III tumor. Postoperatively, the median target dose was 55,5 Gy to the tumor region. Additional RT to the regional lymph nodes was applied in 7 pts. with a median target dose of 54 Gy.

**Results:** With a follow-up of 4 to 112 months (median 22 months) the median overall survival (OS) after first diagnosis was 32 months (95%-CI: 0-75 months) with a 3-year OS rate of 47% (95%-CI: 25-69%). 6/31 pts. relapsed locally after a median of 4 months, 10/31 pts. developed regional lymph node metastases, and 7/31 pts. distant metastases. 9 pts. died as a direct result of MCC. Locoregional control and disease-free survival were significantly improved for pts. with postoperative RT (p=0.023). Uni- and multivariate analysis revealed that tumor locations in the head and neck and the lack of postoperative RT are unfavorable prognostic factors.

**Conclusion:** Postoperative RT to the primary tumor region and regional lymphatics reduces significantly the risk for locoregional recurrence, especially for head and neck MCC. Prospective clinical trials should be performed to confirm these observations.

730 POSTER

## Osteoradionecrosis of pelvic bones - a single institution experience

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**Purpose:** to assess the incidence and risk factors of pelvic fractures as a result of radiation therapy in women with gynecological cancer.

**Methods and materials:** We retrospectively reviewed 4016 female patients treated at our institute between 1980 and 1998 with megavoltage radiation with or without brachytherapy for cancer in the pelvic area. Eligible were patients with vulvar, vaginal, cervical, endometrial and Fallopian tube cancer. Median follow-up was 88 months (range 0-240). Emphasis was put on treatment-related and patient-related risk factors.

**Results:** 15 patients developed symptomatic bone fracture caused by osteoradionecrosis, which makes an overall incidence of 0,37 per cent. The diagnosis was based on anamnesis, clinical course and X-ray or CT