**951** POSTER

**Enhanced sensitivity of human ovarian carcinoma cell lines A2780 and A2780/CP to the combination of cisplatin and synthetic isothiocyanate ethyl 4-isothiocyanatobutanoate E-4IB**

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Naturally occurring and synthetic isothiocyanates (ITCs) are known as chemopreventive agents. The present study shows a new synthetic ITC derivate ethyl 4-isothiocyanatobutanoate (E-4IB) as an effective modulator of cellular proliferation and apoptosis with potential utility as an anticancer drug, as well as a sensitizer to routinely used chemotherapeutic agent cisplatin (CP).
We evaluated the growth inhibitory effects of E-4IB on the human ovarian carcinoma cell line A2780 and its cisplatin-resistant variant A2780/CP using MTT-test and its apoptosis-inducing properties by flow cytometry: FDA-analysis and DNA-analysis.
Effect of E-4IB was assessed both alone and in paired combination with cisplatin. Combination index (CI) values from Calcusyn 1.1 (Biosoft, 1996) were used to characterize the interactions as synergistic, additive, or antagonistic. Significant synergistic effect of E-4IB (0.5–5 μM) with CP (2.5–10 μM) on A2780 parental cell line (CI from 0.39 to 0.75) was observed also on A2780/CP resistant subline, although to a lesser extent (CI from 0.43 to 0.86) for CP concentrations 5–25 μM and the same concentrations of E-4IB. Synergy in growth inhibition correlated with the potential of E-4IB to stimulate apoptosis induced by CP (from 9.5% to 24.7% at 24 hours) while E-4IB alone induced 3.6% of apoptotic cells in A2780 cell line.
We conclude that E-4IB may be worth of further studies assessing its value in the ovarian carcinoma treatment, in combination with the other chemotherapeutic agents.

## *Publication*
## Gynaecological cancer

**952** PUBLICATION

**Long-term results of radiotherapy for recurrent cervical carcinoma following surgery**

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**Introduction:** Therapeutic options for recurrent cervical cancer following initial surgical treatment are pelvic exenteration or radiotherapy. Based on a small number of retrospective studies, 5-year survival rates may range from 0% for patients with large recurrences extending to the pelvic wall to 77% for highly selected patients with small central tumours. Aim of the present study was to investigate long-term outcome and prognostic factors in patients treated by radiotherapy in our institute.
**Patients and methods:** From 1970 to 2004, 35 patients (median age: 46 years; range 24–80 years) were treated by high-dose radiotherapy for a locoregional recurrence following initial radical locoregional surgery. Median time to recurrence after surgery was 1.6 years (range 0.13–34 years). Histological diagnoses were adenocarcinoma in 5 patients and squamous cell carcinoma in 30 patients. Thirteen patients had a central recurrence, 22 patients had extension to the pelvic wall. All patients received external beam radiotherapy (EBRT) to the whole pelvis (39.5–53 Gy, median dose 45 Gy, fraction dose 1.8–2 Gy), followed by a boost to the tumour by either EBRT (5.4–30 Gy, median dose 15.2 Gy, fraction dose 1.8–2 Gy) or LDR brachytherapy (10–58 Gy in 1–3 applications, median dose 20 Gy).
**Results:** After a median follow-up period of 10.9 years, actuarial 1-, 5-, 10- and 15 year overall survival rates were 74%, 42%, 31% and 26%, respectively. Actuarial 1-, 5-, 10- and 15-year disease free survival rates were 68%, 44% and 40% and 40%, respectively. Nine patients had a relapse in the treatment field, 9 developed distant metastases, and 1 patient had a pelvic relapse and distant metastases. Actuarial 1-, 5- and 10 year overall survival rates for patients with a recurrence extending to the pelvic wall were 63%, 26% and 13% compared to 92%, 67% and 58% for central recurrences (median survival 1.7 years compared to 12.8 years, $p = 0.01$). Patients treated for a recurrence more than 1 year after surgery had a median overall survival of 6.7 years, compared to 0.9 years for patients relapsing within 1 year ($p = 0.02$). Histology was not a significant factor for overall or disease-free survival.
**Conclusion:** Our long-term data suggest that high-dose radiotherapy for recurrent cervical carcinoma following surgery is an effective treatment strategy which can achieve long-term survival, even in patients with a recurrence extending to the pelvic wall.

**953** PUBLICATION

**Local control in definitive MRI based radiotherapy of cervix cancer: Vienna experience in 145 patients treated by intracavitary ± interstitial brachytherapy from 1998–2003**

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**Introduction:** To evaluate, if intracavitary ± interstitial cervix cancer brachytherapy based on systematic MRI assisted treatment planning improves local control, without increasing late side effects. Clinical results of two patient cohorts are analysed treated at Vienna University within the same clinical setting, in two consecutive time periods with evolving approaches in MRI assisted treatment planning and performance.
**Material and methods:** The study includes 145 consecutive cervical cancer patients (median age 60 yrs (26–92)) who received definitive radiotherapy (45 Gy EBT) ± weekly cis-Platin based chemotherapy (40 mg/m$^2$) at Medical University of Vienna from 1998–2003. FIGO stage distribution was: I = 14, II = 87, III = 37, IVA = 7. In 78 patients tumour size was larger than 5 cm. Brachytherapy was intracavitary in 116 pts. and intracavitary+interstitial in 29 pts.. A dose of $4 \times 7$ Gy was prescribed to point A from 98–2000 (group A: 73pts.) and to a High Risk-CTV (Haie-Meder et al. R&O 2005) from 2001–2003 (group B: 72 pts.), respectively, corresponding to 84 Gy EQD2 ($\alpha/\beta 10$).
MRI assisted treatment planning was carried out in all patients, 1–2 out of 4 fractions in group A, all fractions in group B. In group B, systematic individualised MRI based treatment planning was performed for each fraction, with contouring of GTV, HR-CTV, bladder, sigma, and rectum and prospective evaluation of dose volume parameters for HR-CTV (D90, D100) and organs at risk (0.1, 1, 2 cc), using the linear-quadratic model. In group A, no systematic MRI based planning was carried out because of missing comprehensive concepts for target contouring, DVH analysis, and biological modelling. Late adverse side effects were evaluated according to LENT-SOMA score. Median follow up for surviving patients was 39 months. Kaplan-Meier method and log-rank test was used for statistical analysis.
**Results:** Complete response at 3 months after treatment based on MRI and clinical findings was achieved in 138 out of 145 pts (95%). After median 39 months follow up, 15 recurrences were observed within the true pelvis: group A 11 local recurrences (LR), group B 4 LR. Actuarial 3 yrs continuous complete remission (CCR) rate was 88% (total 15 LR), actuarial local control (LC) rate 85% (total 22 LR) (Table 1). Overall, 8 late genitourinary and digestive grade 3 and 4 adverse late side effects were observed, 6 in group A and 2 in group B.

Table 1: Actuarial continuous complete remission rate at 3 years and absolute total number of local recurrences (LR)

| Tumor size | Vienna 93–97* n = 189 | Group A: 98–00 n = 73 | Group B: 01–03 n = 72 |
|---|---|---|---|
| Overall (LR) | 78% (25) | 83% (11) | 95% (4) |
| <5 cm (LR) | 90% (4) | 96% (1) | 100% (0) |
| * 5 cm (LR) | 67% (21) | 72% (10) | 91% (4) |

* (Pötter et al. Cancer Radioth 2000)

**Conclusion:** The clinical results of two approaches with evolving concepts in MRI based treatment planning and performance supported by growing clinical experience indicate the following: Systematic individualised MRI assisted treatment planning including GTV and HR CTV contouring, DVH analysis and biological modelling with additional interstitial brachytherapy in advanced disease improves within an experienced clinical setting significantly local CCR in cervix cancer, while the rate of late adverse side effects remains small. Without a systematic approach no significant improvement was achieved during the "learning period" by using MRI. Evaluation of results with regard to dose-volume-effects and survival parameters are needed to further explore the potential of 3D MRI based gynaecological brachytherapy.

**954** PUBLICATION

**Clinical-sonography scoring system in noninvasive diagnosis of endometrial cancer**

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**Background:** Cancer of the endometrium accounts for 6–7% of all cancers in women. In 90% of all endometrial cancers vaginal bleeding is the leading clinical symptom, but only 25% of all postmenopausal bleeding is

caused by endometrial cancer. Nowadays, scoring systems have become acceptable in medicine as less invasive, adequate, and precise diagnostic method. The main goal of this study was to exame statistical significance of clinical-sonography scoring system as a noninvasive diagnostic method for endometrial cancer.
**Material and methods:** It was a prospective study and 122 patients with postmenopausal bleeding were included. Transvaginal sonography was performed before curettage. Patients were divided into the two groups (A and B), after final histopathological findings obtained by curettage. Group A consisted of patients with endometrial cancers and group B of patients without endometrial malignancy. Clinical-sonography scoring system named ONKO 1 have been created. Each patient got her own score by using the parameters for scoring systems obtained by anamnesis, clinical exam, and transvaginal ultrasonography. Evaluations of these clinical-sonography scoring systems were performed by using test for diagnostic accuracy and receiver operating characteristic (ROC) curve.
**Results:** Patients with endometrial cancer were older: 64.49 vs. 58.81 years, length of corpus uterus was longer: 6.41 vs. 5.25 cm, and postmenopausal period was longer: 13.67 vs. 9.11 years. All parameters were statistically significant. Average value of clinical-sonography scoring system ONKO 1 in group A was 9.14, SD $\pm$ 2.32 and in group B was 7.13, SD $\pm$ 3.07. There was found statistically significant difference between group A and group B of patients using this scoring system.
**Conclusion:** Postmenopausal bleeding caused by endometrial cancer is usually diagnosed in older patients. It was possible to distinguish high risk patients with neoplasia from those with benign changes of endometrium using the clinical-sonography systems ONKO 1. There was statistically significant difference between scoring values of these groups of patients."Cut-off" value was *6 for ONKO 1 scoring system. Nevertheless, histopathological examination is still unavoidable in final diagnosis of endometrial cancer.

**955** PUBLICATION

**Efficacy and safety of combined radiotherapy with irinotecan (CPT-11), interferon (IFN-alpha-2b) and amifostine in patients with locally advanced cervical carcinoma**

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**Introduction:** In patients with Locally Advanced Cervical Carcinoma, there has been an increasing interest in combining conventional radiotherapy (RT) with chemo-sensitizing agents such as irinotecan (CPT-11) and interferon a2b (IFN-$\alpha$-2b). Toxicity is always increased with chemo-radiation, which might affect the treatment gain. Amifostine significantly reduces acute and late chemoradiation induced toxicities. The purpose of this study was to evaluate the efficacy and safety of the combined treatment.
**Material and methods:** 47 patients with Locally Advanced Cervical Carcinoma St IIb(33), St IIIa(3) and St IIIb (11) entered this study. The median age was 57 years (range 36–78). The patients received standard fractionated RT (1.8 Gy/fraction, 5 days/week) for six consecutive weeks (median dose 54.0 Gy), CPT-11 (30 mg/m* iv on day 1 of each RT week) and IFN-$\alpha$-2b (3MU/3 TIW sc) during the whole radiation treatment. Additional intracavity treatment with CS137 (20 Gy) was given. Amifostine was administered at a flat dose of 500 mg iv prior to each RT fraction. Patients were evaluated for response six weeks after the completion of at least 4 cycles of biochemo-radiotherapy.
**Results:** Until now 36 of 47 patients were evaluated for clinical response. 11 patients were non-valuable due to: Refusal to the treatment plan (4 pts), increased toxicity (5 pts), non-completion of the treatment schedule to date (1 pt) and death due to inter-current disease (1 pt). All patients received amifostine as scheduled except 2 pts to whom the administration was interrupted due to hypotension (1 pt) and emesis (1 pt).
Complete response was present in 23 patients (64.0%), partial response in 7 patients (19.4%) and in 6 patients (16.6%) progressive disease was present. Of the 23 patients that have shown clinical complete response, 10 patients underwent hysterosalpingo-oophorectomy (8 pts StIIb, 25 pts St IIIb). 8 patients of them have shown pathological complete response, while 2 patients have shown pathological partial response. Median overall survival was 22 + months.
46 patients were valuable for toxicity grade 3–4. Hematological toxicity (6/46 pts, 13.04%) and intestinal mucositis (6/46 pts 13.04%).
**Conclusion:** The combination of standard fractionated RT with concurrent administration of CPT-11 and IFN-á2b in patients with Locally Advanced Cervical Carcinoma is highly active and well tolerated treatment. The use of amifostine before RT is well tolerated and is clinically beneficial concerning the chemo-radiation toxicities.

**956** PUBLICATION

**Radiotherapy in the adjuvant setting of cervical carcinoma: Treatment results and prognostic factors**

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**Background:** To evaluate the efficacy of postoperative radiotherapy and to investigate prognostic factors for early stage cervical cancer patients.
**Methods:** From December 1993 to December 2001, 157 patients with stage I-II cervical cancer treated by surgery and postoperative radiotherapy were included in this study. Indications for postoperative external radiotherapy were based on pathological findings, including lymph node metastasis, positive surgical margins, parametrical involvement, pT2 tumor and presence of any 2 minor risk factors like lymph vascular space involvement, deep stoma invasion and tumor diameter between 2–4 cm. Seventy-two (46%) patients received radiotherapy (RT) alone, whereas 68 (43%) were treated with RT and concomitant chemotherapy (CT) and 17 received neoadjuvant CT. Patients with positive vaginal margins also received 27.5 Gy HDR brachytherapy in 5 fractions.
**Results:** Median follow-up time was 43 months. The actuarial 5-year overall (OS) disease free (DFS), local recurrence free (LRFS) and distant metastases free (DMFS) survival rates were 72%, 68%, 76% and 87% respectively. Univariate and multivariate analyses revealed that metastatic lymph node (LN) level was the unique significant prognostic factor for all end points and concomitant CT was another significant factor for all end points except DMFS. Number of metastatic pelvic LN for LRFS, RT duration for DFS and LRFS and tumor diameter and type of surgery for DMFS were the other significant prognostic factors that affect survival rates in multivariate analyses. Based on the tumor related prognostic factors, we defined 2 groups as Intermediate risk group (no LN metastasis or with positive 1–3 obturator LN metastases) or high risk group (with positive common iliac LN metastases or more than 3 positive LN metastases). Significant differences were found between these risk groups in terms of OS, DFS and LRFS. Concomitant chemotherapy produced significantly better survival rates in intermediate risk group, whereas no significant benefit could be found in high risk group.
**Conclusion:** Our results indicate that level and number of metastatic LN's are the most important prognostic factors determining the survival rates and patients with upper lymphatic involvement or more than 3 metastatic LN, it seems concomitant CT is not adequate for patients with upper lymph node involvement or more than 3 metastatic LN.

**957** PUBLICATION

**Cell proliferative activity in endometrial cancer: 5-year follow-up**

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**Purpose:** The purpose of the study was to research flow cytometry characteristics in endometrial cancer.
**Methods:** Flow cytometry characteristics (EPICS-XL, Coulter, USA): tumor cell ploidy, cells quantity in G0/G1, S and G2+M, iDNA, aneuploid cells quantity, and proliferative index (IP) were studied in 102 patients with endometrial cancer I-IV stages (FIGO) (mean age 59.7). Median follow-up was 62 months.
**Results:** Stage I endometrial cancer was diagnosed in 82 (80.4%) patients, stage II – in 8 (7.8%), stage III – in 11 (10.8%), and stage IV – in 1 (1.0%). Sixty-eight patients (66.7%) had endometrioid adenocarcinoma, 23 (22.5%) – adenocarcinoma with squamous differentiation. Sixty-seven patients (64.7%) had aneuploid tumors. Most patients with aneuploid tumors had iDNA = 1.1 – 1.76. Mean G0/G1 content was 81.7$\pm$0.8%, S – 9.6$\pm$0,5%, G2+M – 8.7$\pm$0.7%, IP 18.3$\pm$0.8%. Aneuploid endometrial cancer was diagnosed significantly more often in patients older than 70 years, in advanced cases, grade 2–3 tumors, tumors with deep (>1/2) myometrial invasion, cervical and intraperitoneal involvement, adnexal and lymph node metastases, and lymph-vascular space invasion ($p < 0.05$). There was positive correlation between mean G0/G1, S, G2+M content