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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

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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.

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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 4×7 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.

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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