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INCIDENCE OF EMESIS AND NAUSEA IN FRACTIONATED RADIOTHERAPY PATIENTS

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The findings of a large, multicentre assessment involving 1387 patients undergoing fractionated radiotherapy, between thorax and pelvis, demonstrated that few patients receive anti-emetic prophylaxis (≈15%). A subgroup of patients (n = 297) consented to complete the patient specific assessments recording daily their emesis and nausea; 269 patients (Group I) who had received no anti-emetic prophylaxis (normal emetogenic risk) and 28 patients (Group II) who had received prophylactic anti-emetic regimens not containing a 5-HT_3 receptor antagonist (elevated emetogenic risk). In Group I, 38% of patients experienced moderate/severe nausea, and 36% experienced emesis with 47% of patients experiencing both symptoms. Despite anti-emetic prophylaxis, 61% of patients in Group II experienced moderate/severe nausea and 57% experienced emesis with 75% of patients experiencing both symptoms. Twenty four percent of patients who completed the assessment received anti-emetic medication as treatment/rescue on at least one day of their course of fractionated radiotherapy. As expected the higher the dose per fraction of radiotherapy, the earlier in the course of radiotherapy patients received treatment/rescue anti-emetic medication. This assessment confirmed that the majority of patients receiving fractionated radiotherapy do not receive anti-emetic prophylaxis, although a significant proportion of patients experience emesis and nausea. In addition there is a need for more effective anti-emetic prophylaxis.

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MULTIVARIATE ANALYSIS OF COMPLICATIONS OF RADIOTHERAPY ALONE IN CERVIX CANCERS

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From 1970 to 1993, 632 patients with carcinomas of intact uterine cervix were treated with radiotherapy alone. The aim of the study is: (1) to describe all types of late normal tissue damage using French Italian syllabus. (2) to determine by univariate and multivariate analysis the predictive factors of rectal, bladder, colon, small bowel, genitalia and soft tissues severe sequelae (G3G4). *Results:* The distribution of sequelae and complications is: G1 23%, G2 18%, G3 6%, G4 2.5%. The distribution of G3G4 per organ is: Genitalia 6% (no G4), rectum 4%, colon 1.5%, bladder 1.2%, soft tissues 1%, small bowel 0.5%. Univariate analysis shows an increased risk of G3G4 rectal complications according to Figo substaging, external radiation dose above 40 Gy (ED), parametrium boost (PB), use of brachytherapy vaginal cylinders applicator (CA), high HWT or mean rectal dose rate. Bladder severe sequelae correlate with increased of Figo, ED, PB, CA, ICRU bladder dose and bladder maximum dose rate. The five main factors influencing the genitalia and soft tissues sequelae are Figo, ED, PB, CA and HWT. In multivariate analysis, CA remains the only predictive factor for G3G4 bladder events (odds ratio OR = 10.8); the mean dose rate increase, CA and Figo are predictive of severe rectal sequelae. Prevention of complications based upon individual changes of treatment planning according to dosimetry parameters led to a sharp decrease in severe complications with time (19% before 1978, 14% between 1978–1983, 6% after 1983). No lethal complications occurred after 1983. Five year specific and disease free survival rates per stage of patients treated during each period are similar.

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DEFINITIVE EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER. RESULTS OF 230 TREATED PATIENTS IN ONE CENTER

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No randomized trials of the various treatment options for localized prostate cancer have been reported. Therefore, radical prostatectomy and definitive radiotherapy are competing management options. To define the potential radiocurability for localized prostate cancer a series of 230 pts treated with external beam irradiation (1981–1991) was analyzed.

All pts had histologically proven adenocarcinomas with staging according to the UICC-classification. There were 32 T1-, 71 T2-, 110 T3-, and 7 T4-carcinomas. A moderate differentiation showed 109 tumors, and a poor differentiation 43 tumors. Radiotherapy was applied by 8-MeV-photons of a linear accelerator. With computerized treatment planning, treatment volume included the prostate, paraprostatic and pelvic lymph nodes up to 45 Gy and was continued with shrinking fields up to 54 Gy to the prostate and paraprostatic tissues. Finally a boost with bisectional rotating was given up to a total dose of 66–70 Gy (1.8–2 Gy daily).

All pts are evaluable for response with a median follow-up of 60 months. Median age at diagnosis was 69 y. Overall 5- and 10-year survival rates are 67% and 46%. Disease-free 5- and 10 y-survival is 59% and 50% for T2-, and 56% and 37% for T3-carcinomas. 15% pts developed locoregional recurrence. This study reveals high effectiveness of definitive external radiotherapy for locoregional control of prostate cancer.

Ovarian tumours

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ADJUVANT RADIOTHERAPY IN STAGE I OVARIAN CANCER

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The retrospective analysis of 141 patients with stage I ovarian cancer registered in the Institute of Oncology in Gliwice from January 1985 to December 1991 was undertaken. Subsequent to the surgery 91 patients were treated by external magavoltage irradiation and 50 had no further treatment. There was no significant difference between the groups with the respect to stage and histological grade distribution. In radiotherapy group 13% developed recurrent disease comparing to 12% in control group. Adjuvant radiotherapy had no benefit in terms of relapse rate and survival. Multivariate analysis showed that dose of irradiation and the irradiated volume did not influence the prognosis.

Histological grade followed by stage were the major predictors for relapse and significantly correlated with survival.

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A DOSE INTENSITY STUDY OF CARBOPLATIN IN OVARIAN CANCER

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It is still discussed if there is a benefit of increasing the dose of platin in the treatment of ovarian cancer. In 1991 The Danish Ovarian Cancer Group (DACOVA) started a study to address this problem.

Patients with epithelial ovarian cancer stages II–IV were randomized to receive Carboplatin AUC = 4 versus AUC = 8 as calculated by Calvert's formula and the same dose of cyclophosphamide (500 mg/m^2). The treatment was given every 4 weeks for 6 cycles. The accrual was stopped in July 1994 and 222 patients were allocated. Fifty per cent underwent second-look laparotomy. The frequency of complete pathological remission was 16% and 15% and the median survival was 11 and 14 months for standard and high dose regimen respectively. Survival rate at 3 years was 30% and 33% respectively. The side effects were manageable in both arms and there were no treatment related deaths. The frequency of grade 3 and 4 bone marrow toxicity was significantly higher in the AUC8 arm.

In conclusion the increase of Carboplatin dose intensity did not improve the antineoplastic effect to any noticeable extent. Further increase of dose intensity cannot be performed without growth factor or stem cell support.

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CARBOPLATIN AND OVARIAN CANCER IN THE ELDERLY

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In western Europe 25% of the population is aged aver 70 years. Half of the new malignancies occur in this group, in general poorly treated. The risk of increased toxicity in relation to the impaired visceral functions, notably renal, requires an individual adjustment of the posology. We have studied the possibility of adjusting the posology of Carboplatin (CBDCA) according to the formula of Calvert: CBDCA DOSE (MG) = 5 (GFR + 25). From Jan. 93 to Dec. 94, 16 elderly women aged between 72 to 85 years with a stage III or IV ovarian carcinoma in good general heath (PS. OMS 0–2) were treated as out-patients by the combination of Carboplatin-Cyclophosphamide every 4 weeks. The number of courses of treatment carried out was between 2 and 6 per patient. An objective response greater than 50% was observed in 14 patients and 2 progressive diseases. 3 patients (73–78 years) have undergone a 2e look and treated by 6 courses of Taxol 175 mg/m^2 every 3 weeks. No grade IV toxicity no hospitalisation due to toxicity.

In conclusion: elderly people should be treated no differently from other age groups, to relieve symptoms, and achieve a cure where possible

—the quality of life must be in mind

—clinical trials should be extended to the elderly.

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TUMOR BULK, HISTOLOGY, AND BASELINE HEMOGLOBIN MAY INFLUENCE RESPONSE (RR) IN PLATINUM PRETREATED OVARIAN CANCER (OVCA)

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Time from last chemotherapy is a well known predictor of RR to 2nd line treatment in relapsed OVCA. Little is known about other tumor or patient (pt) related factors that may be of relevance. For that reason, a multifactor analysis of RR predictors was undertaken in 382 pts enrolled in a European-Canadian trial of 2nd/3rd line paclitaxel. Serous histology, maximum tumor bulk < 5 cm and normal hemoglobin (Hgb) were identified as significant predictors of RR in the final model. To determine if these factors might be of predictive value with other agents, 105 OVCA pts given 2nd line high dose epirubicin in an EORTC GCCG trial were analysed. Results are as shown:

		paclitaxel		high dose epirubicin	
		RR	p value+	RR	p value*
Histology	serous	20.7%	.05	23%	NS
	other	11.8%		17.5%	
tumor	<5 cm	23.9%	.006	23.5%	NS
	>5 cm	12.1%		18.9%	
Hgb	normal	20.7%	.02	23.9%	NS
	low	9.6%		18.6%	
time	<12 mo	15.6%	NS	15.9%	.017
	>12 mo	22.1%		39.1%	

+ final model; *univariate (multifactor analysis not done since only one factor had $P < .05$)

While only time from last treatment reached significance in the EORTC trial, the RR by histology, size and Hgb show the same trends as the paclitaxel trial. Results on other agents will be presented. If higher RR in low bulk disease is consistently noted, a trial of early intervention in relapsed OVCA may be indicated.

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SAFETY AND EFFICACY OF TAXOL® (PACLITAXEL) OVER 3 H IN 306 PLATINUM-REFRACTORY PATIENTS WITH OVARIAN CANCER: RESULTS OF A GERMAN COOPERATIVE STUDY

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We present a phase II study with TAXOL® (Paclitaxel) in 306 patients (pts) with advanced ovarian cancer, who relapsed after at least one platinum based chemotherapy (CT). Objectives are safety and toxicity. Pts received 175 mg/m^2, when pretreated with 1–2 prior CT regimens (Group A: 212 pts, 69.3%) and 135 mg/m^2 with 3 and more CT regimens (Group B: 94 pts, 26.4%) by 3 h-infusion every 3 weeks after standard premedication with steroid, antihistamine and H_2-blocker. The median age was 56 at a performance status of ECOG = 0 in 57.5%, ECOG = 1 in 34.0% and ECOG = 2 in 8.5% of the pts; median time from last CT was 107 days (15–3066). The total number of cycles was 1774, the median number per pt was 6 cycles.

For toxicity data 1202 cycles were evaluated. The main toxicity was neutropenia with higher incidence at 175 mg/m^2 (WHO 1 + 2: group A: 63.3%, group B: 71.2%, WHO 3 + 4: group A:36.7%, group B: 28.8%;), which is not statistically significant.

Thrombocytopenia: WHO 1 + 2: A: 1.8%, B: 1.3% WHO 3 + 4: A: 15.7%, B: 13.8%.

Anemia: WHO 1 + 2: A: 17.8%, B: 19.9%. WHO 3 + 4: A: 1.8%, B: 1.2%.

Non-hematological toxicities were minimal:

Arthralgia/myalgia: WHO 1 + 2: A: 19.1%, B: 14.0%. WHO 3 + 4: A: 2.4%, B: 2.6%

Peripheral neuropathy: WHO 1 + 2 A: 36.0%, B: 19.2%. WHO 3 + 4: A: 0.4%, B: 0.9%.

Alopecia.: WHO 1 + 2: A: 26.7%, B: 24.2%. WHO 3 + 4: A: 69.5%, B: 71.7%.

Hypersensitivitity reactions: WHO 1 + 2: A: 17.2%, B: 8.3%. WHO 3 + 4: A: 0.3%. B: 0.0%.

295 pts could be evaluated for response: complete response (CR): 28 pts (9.5%), partial response (PR): 57 pts (19.3%); stable disease (SD): 119 pts (40.3%) and 85 pts (28.8%) with progression.

This study confirmed the efficacy and tolerability of TAXOL®, administered as 3-h-infusion after premedication, in the treatment of platinum-refractory ovarian cancer. Main toxicity was neutropenia without severe clinical manifestations. The encouraging response rate for these heavily pretreated patients will lead to further studies in first-line ovarian cancer.

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CLINICAL RESULTS OF A NEW APPROACH OF THERAPY OF OVARIAN CANCER: RETARGETING OF T CELL CYTOTOXICITY BY BISPECIFIC ANTIBODIES

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We propose specific retargeting of *in vitro* activated PBMC by an anti FBP/antiCD3 bsAb (OCTR) as an alternative to second-line conventional treatment of ovarian carcinoma. 28 patients with limited i.p. disease after surgical debulking were studied. They received 2 i.p. 5-day cycles of activated PBMC retargeted with OCTR plus low-dose r-IL2. Despite unfavorable tumor characteristics i.p. CR or PR in 9 of 27 patients (33%) were demonstrated by strict surgicopathologic evaluation methods. In most of the responding patients, the disease relapsed outside the peritoneal cavity and in 2 cases CR i.p. were accompanied by progression in retroperitoneal lymph nodes, suggesting that this form of treatment is active in a local fashion.

To possibly cure extra peritoneal disease, we started clinical safety studies to establish the appropriate dosages of i.v. infusion of OCTR coated T-lymphocytes. In 3 patients which received simultaneous i.v. and i.p. infusions, signs or symptoms were not significantly different from those observed after i.p. treatment. Immunological monitoring and clinical evaluation are ongoing. Partially supported by CNR-ACRO end AIRC.