for cases lost to follow-up): St. I-24/27 (89%) v. 14/16 (88%), St. II-24/31 (77%) v. 28/36 (78%), St. III – 8/27 (30%) v. 10/22 (45%), St. IV – 0/3 (–) v. 0/4 (–) and all stages – 56/88 (64%) v. 52/78 (67%). Late post-irradiation sequelae were (French-Italian glossary): G1-20% v. 14%, G2 – 8% v. 10%, G3 – 10% v. 7%, G4 – 4% v. 1% and total – 42% v. 32%.

Conclusion: ≥4-year survival of stage III was better in Co-60 group and late postirradiation complications were more frequent in Ir-192 group of patients.

927 POSTER

Phase II trial of paclitaxel and cisplatin in advanced or recurrent adenocarcinoma of the endometrium

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Purpose: To evaluate to activity and toxicity of the combination of paclitaxel with cisplatin in patients with primary stage IV or recurrent endometrial adenocarcinoma.

Methods: The treatment consisted of paclitaxel 175 mg/m^2 IV over 3 hours followed by cisplatin 75 mg/m^2 every 3 weeks for a total of 6 courses.

Results: Twenty-four patients were included. The median age was 62 years (range: 45 to 75 years). Histology consisted of endometrioid adenocarcinoma in 16 patients, the median PS was 1 and twelve patients had previously received radiotherapy. Objective response was documented in 16 patients (67%) including 7 complete and 9 partial responses. The median remission duration was 7 months, the median time to progression was 8 months and the median overall survival was 21 months. Grade 3 or 4 toxicities consisted of neutropenia in 22%, neurotoxicity in 13%, and nausea and vomiting in 9%. No patient died due to toxicity.

Conclusions: The combination of paclitaxel and cisplatin is a relatively well tolerated and active regimen for the treatment of patients with advanced or recurrent endometrial cancer.

928 POSTER

Combined radio-chemotherapy (CR) in advanced cervical cancer: A phase-II trial with cisplatin and bleomycin

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Cancer of the cervix is the first or second most common form of cancer in the female population in developing or poor countries. It is the one of the most frequent malignancies in Bosnia and Herzegovina since the war. The problem of large numbers of young women with late diagnosis, and advanced stage tumors is compounded by the poor results of conventional therapy.

In our efforts to prevent high frequency of pelvic recurrences and distant metastasis, we performed single Institution study, in which from January 1997 to June 1998, 25 previously untreated women with advanced cervical cancer were treated with a therapy consisting of fractionated external beam irradiation (45 Gy), administered using 1.8–2.0 Gy/day, 5 days a week, to the whole pelvis with local boost if indicated, followed by two intracavitary cesium (Cs) applications (2 × 15 Gy), combined with cisplatin (50 mg m−2) and bleomycin (20 mg m−2). Cytotoxic agents were given intravenously on every 3 weeks for a total of four courses during the irradiation. The patients ages ranged from 34 to 52 years, median 49 years. There were 11 FIGO stage IIB, 2 IIIA, 11 IIIB, and 1 IVA. Acute toxicities (g WHO grade 2) were leucopenia (14 of 25 patients), diarrhoea (10/25), cystitis (2/25), abdominal pain (19/25), nausea (13/25) and skin desquamation (10/25). Clinically diagnosed pelvic response was achieved in 84.0% (21/25) with a complete response of 32.0% (8/25). As yet, after a median follow-up of 11.2 months, 21 of 25 patients (84.0%) are alive and well (persistent complete/partial remission), two patients (8.0%) are alive with local progression, two (8.0%) have died from pelvic and/or distal recurrence.

Concomitant cisplatin and bleomycin and radiotherapy is a safe and tolerable mean of treatment for locally advanced cervical cancer. The true advantage for survival, however, can be demonstrated only after completion of randomised trials comparing CR with conventional radiation therapy which is in plan to be performed on our Institute.

929 POSTER

Neoadjuvant chemotherapy in locally advanced cervical carcinoma (LACC): Mitomycin C (M), bleomycin (B) and cisplatin (C) combination (MBC)

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Objective: To evaluate the toxicity and efficacy of MBC in pts with squamous cell LACC.

Methods: Between January 1993 and June 1998, 43 pts with squamous cell LACC were treated with MBC: Mitomycin 10 mg/mq d1, Bleomycin 15 IU d1–3 and Cisplatin 40 mg/mq d1–3, repeated every 3 weeks for 3 cycles, prior to radical histerectomy plus pelvic lymphadenectomy. Eligible pts had histologically confirmed squamous cell carcinoma of the cervix, age =/< 70 years, ECOG PS =/< 2 and adequate pulmonary, hematopoietic, liver and renal function, FIGO Stage IIB, IIA and IIIB, no prior chemotherapy (CT) or radiotherapy (RT) and measurable or evaluable disease by CT scan. Pts received 3 cycles and were the assessed for feasibility of surgery.

Results: 43 pts were included, and 41 were evaluable for response and toxicity. Median age 51.3 years (range 24–70). After NCT, partial objective response was achieved in 28/41 (68.3%) pts and radical histerectomy was possible in 5/42 (11.9%) pts. 13/42 (30.9%) pts experienced no change. Mean of duration of response in not operable pts was 3.21 months (range 1–5). With a total of 122 cycles, toxicity resulted in ECOG G3-4 myelosupression 10 cycles (8.2%) and gastrointestinal 6 cycles (5.4%). There were no toxic death, and all toxicities were reversible.

Conclusion: MBC is a feasible and well tolerated regimen in LACC, with significant anti-tumor activity and reduced toxicity. Operability can be achieved in 11.9% of cases. Nevertheless, the duration of response in pts who remain not operable after NCT was short.

930 POSTER

Results of treatment in patients with cervical carcinoma Stage II distal B

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From 1985 to 1995, 58 patients with cervical carcinoma with a distal involvement of the parametrium stade IIB were treated with a combination of external irradiation and brachytherapy. Pelvis irradiation (+/– para-aortic area) consisted of 45 Gy delivered in 5 fractions per week of 1.8 Gy. Endocavitary brachytherapy, using the mould technique, delivered 15 Gy within the refeence volume according to the ICRU recommendations. Brachytherapy characteristics: the mean 15 Gy reference volume was 340 cc (139 cc–689 cc). The mean bladder dose was 25 Gy (13 Gy–48 Gy) and the mean maximal rectal dose was 26 Gy (5 Gy–55 Gy). The total reference air kerma was 1.94 cGy/m^2 (0.9 cGy/m^2–3.2 cGy/m^2). The overall 3-year and 5-year survival was 75% and 65%. Four patients presented a non sterilization of the tumor. Nine patients presented a local recurrence: 6 central and 3 lateral pelvic recurrences. Three patients presented grade 3 or 4 complications: 2 urinary complications and 1 digestive complications. In this series of patients with advanded stage IIB disease, a combined therapeutic approach with external irradiation and endocavitary brachytherapy following ICRU recommendations gave good results with a satisfactory local control.

931 POSTER

I–II stage endometrial carcinoma: Is tumoral volume a prognostic factor?

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Purpose: to evaluate retrospectively the impact of the tumoral volume on the outcome in the treatment of endometrial carcinoma in I–II stage.

Material and Methods: from 1/1/85 to 31/12/94 219 patients were admitted in this study; among these, 113 patients received postoperative radiotherapy (isocentric box technique, median dose of 46 Gy (min 40, max 55) with 1.8–2 Gy per fraction. Among the well known prognostic factors we have also analysed the tumoral volume, distinguishing two groups: endometrium infiltrated for more (>1/2) or less (>1/2) than half of its volume. This data is defined on anatomo-pathological macroscopic description of the tumor (extension on endometrial mucosa, diameter of the cancer mass compared to uterine cavity). The group is stratified as follow: for volume

(<1/2) G1 = 29%, G2 = 20%, G3 = 8%, I stage = 54%, II stage = 4%; for volume (>1/2)) G1 = 11%, G2 = 19%, G3 = 27%, I stage = 30%, II stage = 12%. In the (<1/2) group 63% of the patients did not received RT, in the other 32%.

Results: In the whole group, relapses were 16.4% (local 8.7%, distant 6.8%, both 0.9%). The incidence of the local relapses (<1/2) vs (>1/2) is 5% vs 11%, distant relapses 3% vs 11%, NED survival after 60 months is 92% vs 73% (p = 0.0001).

The most important prognostic factors using multivariate analysis are: for Local relapse Vol. >1/2; for Distant relapse G3, Vol. >1/2, stage II; for Mortality G3, Vol. >1/2. Radiation therapy decreases significatively the risk for local relapse

Discussion: in our series tumoral volume seems to be a very important prognostic factor influencing relapse and mortality rates, as showed in the table. Further studies are required to confirm these data, especially using more precise and rigorous criteria in anatomo-pathological analysis.

932 POSTER

8-hydroxydeoxyguanosine in cervical cells DNA: Correlation with HPV infection and grade of dysplasia

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In this study, the 8-OhdG level was assessed in human cervical cells by an immunoperoxidase method and was related to the presence of HPV infection and dysplasia. After optimising the immunohistochemical method in detecting oxidative DNA damage by testing it on AFB1 treated MCF-7, we have used this technique to estimate the oxidative damage in cervical cells collected during a routine PAP tests. 38 women (age range: 20–55, mean age 36.8, s.d. 9.6) were enrolled into the study. After informed consent was obtained, cervical cells were spread on slides precoated with 0.2% poly-D-lysine. Quantitation of specific nuclear staining in AFB1 treated MCF-7 confirmed the ability of the method to detect and differentiate between different damage in a linear dose-related fashion. The analysis of variance (ANOVA) of the data from human samples showed significant differences in standard deviation of the 8-OHdG level between normal, low grade and high grade of dysplasia (p < 0.0001). Comparing the three groups, statistically significant differences were detected between normal and high grade dysplasia (p < 0.001, Bonferroni corrected) and between low grade and high-grade dysplasia (0.003, Bonferrroni corrected), whereas non statistically significant resulted the difference between normal and low grade dysplasia (p = 0.174, Bonferroni corrected). Grouping observations by HPV status, no significant difference was detected in 8-OHdG levels between HPV+ and HPV− subjects (p = 0.8767). The ordered logistic regression analysis showed that while at low 8-OhdG levels the probability of dysplasia was higher for HPV+ subjects, at high 8-OhdG levels the probability of presenting a dysplasia was similar in both HPV− and HPV+ subjects. In conclusion, the immunoperoxidase method, applied to single human cervical cells, provides clear evidences that significant differences exist in 8-OHdG content between normal and dysplastic cells and that oxidative DNA damage might be able to promote cervical carcinogenesis independently by HPV status.

933 POSTER

Phase I study of topotecan (T) with carboplatin (C) alternating with paclitaxel (P) via 3 hour infusion with carboplatin (C) in treatment of newly diagnosed ovarian cancer (OC)

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Objective: Myelosuppression has made it difficult to incorporate T into a triplet with P and a platinum. This study was designed to find the maximum tolerated dose (MTD) of T in combination with C. Alternate cycles of P and C were given to gain exposure to all three active agents.

Methods: C (AUC 5 or 4) was administered first on Day 1 followed by T (0.75 mg/m^2 × 5 days for the first cohort of patients. Due to grade 4 thrombocytopenia, T was reduced to 0.6 mg/m^2 × 3 days and then re-escalated in subsequent cohorts) in cycles 1, 3, 5, and 7. P (175 mg/m^2) was given over 3 hours, then C on Day 1 of cycles 2, 4, 6, and 8. All cycles were to be at 21-day intervals. Dose limiting toxicity (DLT) included: ANC < 500 for >5 days, or grade 4 neutropenia with fever (>38.5 C), platelet count <10,000 or <25,000 with associated bleeding, delay of >7 days in recovery, or non-hematologic toxicity ≥Grade 3. If 1 of 3 patients had a DLT, another 3 were added. If DLT was due to neutropenia or delay in recovery of ANC, granulocyte colony stimulating factor (G-CSF) would be incorporated into the regimen. Due to platelet toxicity at the first dose level, T was changed to a 3-day regimen.

Results: 29 patients enrolled, 27 Stage III, and 2 Stage IV. Ages were 41 to 74 (median 56). A total of 85 cycles were given with the 3-day T. Delays occurred in 33 (39%), but were >7 days in only 11 (13%). 6 cycles were dose reduced. Grade 4 granulocytopenia occurred in 33 cycles (39%), but only 2 cycles (2.3%) were associated with febrile neutropenia. Platelets were <25,000 in 20 cycles (24%), but ≤10,000 in only 7 (8.2%), platelet transfusions were required in 3 cycles.

Conclusions: Myelosuppression is frequent but manageable with T and C. The MTD has not been reached at 1.0 mg/m^2/day. Cummulative toxicity in later cycles will probably prohibit further significant escalation of T.

934 POSTER

Positive progesterone receptor [PR+] and negative estrogen receptor [ER−] expression is associated with improved long term survival in ovarian cancer

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Purpose: Estrogen, progesterone as well as their receptors seem to be involved in the tumorigenesis in ovarian cancer. Their prognostic role is controversial.

Methods: Clinical, histological prognostic factors and steroid receptor status using semiquantitative immunohistochemistry (APAAP-method) were obtained retrospectively from 190 patients' records and stored formalin-fixed, paraffinembedded tumor tissue. Antibodies used: ER (clone 1D5) and PR (polyclonal) both DAKO Hamburg, Germany).

Results: Kaplan-Meier analysis revealed a significant influence of progesterone receptor expression ($P_{Log\ Rank}$ = 0.009) on survival and no influence of estrogen receptor expression. Both steroid receptors were coexpressed (ER+PR+) in 32.6%. ER+PR− tumors were found in 30.0%, ER−PR− tumors in 27.4%, and ER−PR+ in 10.0%. ER−PR+ tumors show a distinct better long-term survival if compared to the other steroid receptor combinations (mean survival 12.9 years; $P_{Log\ Rank}$ = 0.009). Correlation analysis reveals favorable associations between ER−PR+ receptor status and FIGO stage (P_{chi^2} = 0.039) as well as the volume of ascites at the time of primary surgery (P_{chi^2} = 0.069).

Conclusion: The reasons why ER−PR+ ovarian carcinomas are associated with favorable outcome, remain unclear, however, endocrine autoregulative processes, lack of susceptibility to unfavorable influences of estrogen and influences of progesterone, inducing cell differentiation and apoptosis may explain this effect.

935 POSTER

DICEP high dose (HD-DICEP) chemotherapy (CT) with or without peripheral blood stem cell support as consolidation treatment of patients (pts) with advanced epithelial ovarian cancer (AOC)

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Purpose: To analyse the impact and feasibility of consolidation treatment with HD-DICEP on disease-free survival (DFS) and overall survival (OS) in high risk AOC pts.

Patients and Methods: AOC pts (35) entered the study between 1992–1998. All patients were chemosensitive (platinum-CT, +/−taxol) and had low tumor burden at consolidation (determined by surgery in 29/35 pts). High-dose DICEP Seattle-protocol (Proc. ASCO 1993; 12: 50A) was applied. Median PS, 90 (80–100). Median age, 53 years (21–64). FIGO stages: IIIB, 2 pts; IIIC, 18 pts; IV, 6 pts. recurrent disease: 9 pts. Histologic subtype: Serous (S): 13 pts; endometrial (E): 10 pts; undifferentiated (U): 7 pts; mucinous (M) 2 pts; clear cell (C): 1 pts; unclassified (UN): 2 pts. Histologic grade (G): G-III, 22 pts; G-II, 4 pts; G-I, 1 pts; unknown, 8 pts.

Results: With a median follow-up of 51 months (4–75 m), median DFS is 12.5 months (3–68 m+), (median OS not reached). Most pts completed the treatment protocol (62 cycles-cy-/35 pts). 10 pts are long-time disease-free survivors: 2 pts had stage IV-liver parenchymal metastasis (UN: 38 m, and U-GIII: 42 m), 2 pts had recurrences (S-GII: 48 m, S-GIII: 24 m), 5 pts were