1215 POSTER

Outcome and prognostic factors in primary uterine leiomyosarcoma: a rare cancer network study

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Purpose: This retrospective multicentric study aims to assess the outcome and prognostic factors in patients with primary uterine leiomyosarcoma, a rare cancer with a definite pathological identity among the different categories of uterine sarcomas.

Methods: Eighty women, treated between 1980 and 2000 in the member institutions of the Rare Cancer Network, were evaluated. Mean of age was 52 years. Fifty-six patients presented with FIGO stage I, 8 FIGO stage II, 8 FIGO stage III, 4 FIGO stage IV, and in 4 patients the stage could not be determined. Regarding grading, 15 patients had grade 1 or 2 disease, 22 patients grade 3, and in 43 patients grade was not assessed. All patients benefited from a TAH-BSO or from a Wertheim operation. Following surgery, 54 patients were treated with pelvic external beam radiation therapy (EBRT), 15 of them receiving also brachytherapy. Twelve patients received also adjuvant chemotherapy. Median follow-up was 32 months (6-240).

Results: The 5-year overall and disease-free survival were 51% and 37%, whereas the 5-year local and locoregional control were 80% and 72%, respectively. A total of 14 local recurrences, 16 locoregional recurrences, and 38 systemic metastases were observed. In univariate analyses (Log-Rank test) the factors influencing significantly the overall survival were age, FIGO stage, and histological grade. Multivariate analysis (Cox model) revealed that previous uterine surgery (curretage or myomectomy), FIGO stage > I, and grade 3 represented independent adverse prognostic factors. EBRT influenced neither overall survival nor local or locoregional control. Thirty-four patients presented with acute toxicity during EBRT, and 8 patients with late toxicity grade 3 or more. The only factor influencing the development of grade 3 or more late toxicity was the use of brachytherapy.

Conclusions: In our series, patients with stage I and grade 1 or 2 disease had a very good prognosis. Patients with previous uterine surgery had a poor prognosis. Adjuvant radiation therapy did not seem to improve either survival or local control. In addition, brachytherapy increased the treatment-related morbidity. Chemotherapy seemed to increase local and systemic control for advanced stages. The patterns of failure and prognostic factors found in this study could be considered in the overall management of this rare cancer.

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Post-operative HDR bracytherapy and EBT of invasive endometrial carcinoma; Our 25-year experience

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Purpose: At the beginning of 1974. we are started to use high-dose rate brachytherapy and external beam megavoltage teletherapy for uterine (cervix, corpus) carcinoma (Merkaš, Čikarić, Vujnić). From '74 to this time we treated on this way about 30 thousand cases. A retrospective analysis is reported on the results of post-operative irradiation of 526 invasive endometrial carcinoma: St. Ib - 192, St. Ic - 234, St. II a, b - 77 and IIIa, b, c - 23 patients (FIGO).

Methods: HDR brachytherapy (Co-60 or Ir-192): 2 vag. ovoids or vag. cylinder - 4 × 7.5 Gy/0.5 cm, I fraction/w; EBT (x, γ): midplane pelvic dose 30–40 Gy, 15–20 f, 2 parallel opposite pelvic fields without central Pb shield.

Results: Five-year relapse – free survival was: St. Ib - 93.5%, St. Ic - 80.4%, St. IIa, b - 81.8%, At. IIIa, b, c - 61.0% and all stages - 85.0%. Pelvic and vaginal relapses were 2.9%, distant metastases were 2.7% and late postirradiation sequelae were 10.6% (G1 - 6.5%, G2 - 3%, G3 + 4 - 1.1% - French-Italian Glossary).

Conclusion: Post-operative HDR brachytherapy and external beam megavoltage therapy of invasive endometrial carcinoma leads to excellent vaginal and pelvic control with few serious late sequelae. Belgrade results (5-year survival) are statistically significant better than average world results (FIGO annual reports - '88, '91, '94) (5-year survival of all stages: Belgrade vs. FIGO - 85% vs. 65.1%, 69.7% and 72.7%).

1217 POSTER

Results of radiation therapy in the management of vaginal carcinoma

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Purpose: The aim of this study was to evaluate the results of radiotherapy (RT) treatment for vaginal carcinoma at a single institution in the period of 1990-2000. Twenty three patients with a median age of 65 years (range 38-87) were diagnosed during this time with following stages: in situ-1, st I-2, st II-5, st III-5, st IV-10 patients. Twenty out of 23 had RT.

Treatment: The primary treatment was RT in 20 patients, surgery in 2 patients and no treatment in 1 patient. External RT alone in 6 cases, combined with brachytherapy (BT)(cylinder, remote afterloading Co-60 unit) in 8 cases, in 5 cases RT+BT was combined with surgery and one patient had BT alone. The mean external RT dose was 44 Gy (range 36-60 Gy) to the planning target volume and the mean BT dose was 26 Gy (range 10-46 Gy) prescribed to the depth of 2 cm from the middle of the applicator.

Results: One recto-vaginal fistula and one vesico-vaginal fistula in RT+BT+surgery group. Overall disease free survival (DFS) in alive patients is 46 month (11-84 month), overall survival in RT group was 24 month (1-54 month), in RT+BT group 25 month (6-64 month), in RT+BT+surgery group 31 month (11-84 month) and in BT alone group 1 month.

Conclusion: The clinical stage was the most significant prognostic factor, most of the patients were in advanced stages. Other significant factor was histological type (small cell, adeno-mesonephroid). These data showed that the prognosis for vaginal cancer is poor, especially for advanced stages, median survival for stages I-II was 40 month and for stages III-IV 21 month.

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Prognostic significance of microvessel density in endometrial cancer

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Purpose: Tumor angiogenesis is an important step in the progression of cancer and the developement of metastases. Microvessel density (MVD) as a marker of angiogenesis might be of prognostic significance in endometrial cancer.

Methods: Immunostaining was performed on paraffin embedded blocks from 71 endometrial cancer patients using CD31. MVD was calculated using magnification 200x and 400x and compared to other prognostic factors (e.g. tumor size, Grading). Average follow-up was 122 months. Kaplan-Meier analysis and Cox-Regression were used for statistical evaluation of recurrence free (RFS) and overall survival (OS).

Results: During follow-up, 27% of the patients died, 14% because of endometrial cancer. There was a n.s. tendency to longer survival influenced by tumor size, FIGO stage and Grading. No correlation was found when comparing size and FIGO stage to MVD. MVD correlates to Grading (p=0,07; n.s.), but had no influence on overall or disease free survival estimated by Cox regression.

Conclusion: Microvessel density as a marker for angiogenesis correlates to histopathological grading in endometrial cancer, but not to tumor size. Although no correlation to survival was found, angiogenesis may be useful as a target for new therapeutic agents or to optimize radiotherapy.

1219 POSTER

Primary squamous cell carcinoma of the vagina: Experience at the Gustave-Roussy Institute

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Purpose: To analyse the treatment of primary vaginal squamous cell carcinoma (PVSCC) at the Gustave-Roussy Institute between 190 and 1998.

Patients and Methods: 104 patients (pts) of median age 65 years (27–90) were treated for a PVSCC. Forty-three patients had a previous history of hysterectomy (2 pts had cervix carcinoma 22 and 30 years before PVSCC). Stages were (FIGO classification): I (n = 29), II (n = 31), III (n =

32), IVA (n = 8) and IVB (n = 4). Pelvic lymph nodes were present in 24 pts. Squamous cell carcinoma were: grade 1 (40%), 2 (19%) and 3 (41%). Pelvic external beam therapy (EBT) was performed in 99 pts (median total dose = 50 Gy (9–50)) and low dose rate brachytherapy (BT) in 86 pts. BT was delivered in one time (n = 72), 2 times (n = 13) or 3 times (n = 1). Intracavitary irradiation using personalized mould was associated with iridium implants in 32 applications. The median number of sources used for one application was 3 (1–6) with a median total radioactive length of 115 mm. Surgery and chemotherapy were performed in 7 and 5 pts.

Results: Late toxicities were (Franco-Italian Glossary): rectum: grade 1 (n = 8), 2 (n = 8), 2 (n = 0), 3 (n = 1), sigmoid: grade 1 (n = 6), 2 (n = 4), 3 (n = 1), bladder: grade 1 (n = 17), 2 (n = 5), 3 (n = 1), and ureter: grade 1 (n = 2), 2 (n = 1), 3 (n = 1). Response rates after EBT evaluated at the time of BT were: complete response (20%), partial response (57%) and stability (23%). Three months after treatment, complete response rates were 90% for stage I, 90% for stage II, 68% for stage III and 25% for stage TV. The 5-year overall survival rates were: 65% for stage I, 62% for stage II, 35% for stage III and 15% for stage IV. The pattern of failure (first event) were: in the pelvis only (61%), metastatic only (23%) and combined (16%). In a univariate analysis, the age of pts, the stage of tumours, the response to EBT and the duration of treatment were significantly associated with the survival ($p \leq 0.05$).

Conclusion: EBT combined with BT is an effective treatment for pts with PVSCC, particularly Stage I and II. The incidence and severity of late toxicity were relatively low with the use of a customized vaginal mould. The low local control rates in Stage III and IV, and the recent data concerning the treatment of cervix carcinoma suggest the interest of a concomitant radio-chemotherapy in the treatment of PVSCC.

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Evaluation of morbidity after external radiotherapy and intracavitary brachytherapy in patients with carcinoma of the uterine cervix or endometrium

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Early and late radiation morbidity were evaluated according to the RTOG criteria in 771 cervical or endometrial cancer patients who were treated with external radiotherapy (ERT) and intracavitary brachytherapy.

Daily ERT dose was 1.8 Gy.Midline shielding was performed at 50.4 Gy.Total ERT dose was 54 Gy in operated patients and 59.4 Gy in inoperable patients.One fraction of 9.25 Gy was applied to 5-7 mm from the vaginal surface in operated patients and two fractions of 8.5 Gy at weekly intervals were applied to point A in inoperable patients via microSelectron-HDR machine.Four-hundred-seven patients had endometrial cancer and 364 patients had cervical cancer. Two hundred-ten cases with cervical carcinoma had been operated.In patients with endometrial carcinoma total doses at vagina, bladder and rectum were 60.36 Gy, 56.2 Gy and 55.6 Gy respectively. BED for the same points were 79.35, 68.63 and 67.37 respectively for early effects and 123.67, 97.65 and 94.85 for late effects. Acute morbidity rate was 41.5%.Ninety-two patients had grade I,42 had grade II,1 had grade III bladder morbidity;25 had grade I,4 had grade II and 1 had grade III rectal morbidity. Late morbidity rate was 20.9%.Five patients had grade I,11 had grade II,1 had grade III bladder morbidity;2 had grade I,8 had grade II and 2 had grade III rectal morbidity;24 had grade I, 28 had grade II and 4 had Grade III vaginal morbidity.Total doses at vagina,bladder and rectum in operated patients with cervical cancer were 60.51 Gy, 56.53 Gy and 55.67 Gy respectively.BED for the same points were 79.77, 69.36 and 67.52 for early effects; 124.74, 99.3 and 95.17 for late effects. Early morbidity rate was 38.1%.Forty patients had grade I,26 had grade II bladder morbidity;4 had grade I,5 had grade II rectal morbidity and 5 had grade I vaginal morbidity.Late morbidity rate was 30.9%.Five patients had grade I,8 had grade II,2 had grade 3 bladder morbidity;2 had grade I,4 had grade II and 2 had grade III rectal morbidity;19 had grade I,17 had grade II and 6 had grade III vaginal morbidity.Total doses at vagina, bladder and rectum in inoperable patients were 70.92 Gy, 66.71 Gy and 62.38 Gy respectively.BED for these points were 97.43, 89.64 and 81.63 respectively for early effects and 159.3, 143.16 and 126.56 for late effects.Acute morbidity rate was 39% being mostly (95%) grade I or II bladder morbidity.Late morbidity rate was 61.7% being mostly (94%) grade I-III vaginal morbidity.

1221 POSTER

The significance of DNA ploidy, proliferative activity, status of mutant p53 and human papillomavirus type 16 and 18in cervical carcinoma treated by irradiation

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Purpose: To investigate mutual correlation among DNA ploidy, S-phase fraction (SPF), mutant P53, human papillomavirus (HPV) type 16 and 18 and their impact on complete remission (CR), 2 year relapse free (RFS) and 5 year overall survival (OS) rates.

Methods: Archival specimous from 75 irradiated only patients with cervical carcinoma were collected. All patients had a minimum follow-up period of 5 years. Polymerase chain reaction (PCR) and flow cytometry were used to identify the status of HPV 16, 18 and DNA ploidy as well as proliferative activity (SPF with a cut-off value of 10). The semi-quantitative approach was used to identify the presence of mutant P53. The immunohistochemical staining reaction of formalin-fixed, paraffin-embedded specimen was evaluated by assessments of the overall staining intensity and by the fraction of stained cells in percentage categories.

Results: Correlation between potential biologic markers and clinicopathologic factors and treatment outcome revealed that aneuplovd pattern related significantly to a high value of SPF 10 (p = 0.001) which in tern related to a high proportion of positive HPV 18 (p = 0.037) but a relatively low CR rate (p = 0.047). The presence of mutant P53 had no direct impact on pathology, (0.729), stage (p = 0.570), DNA ploidy (p = 0.723), SPF 10 (p = 0.724), HPV 16 (p = 0.113), HPV 18 (p = 0.528) and 5 year OS (p = 0.374). Both of positive HPV 16 and 18 relate to more advanced clinical stage (p = 0.007 and 0.005) while only positive HPV 18 showed a higher proportion of patients with poorly differentiated squamous cell carcinoma & decreased 5 years OS rate comparing to HPV 18 (-) patients (p = 0.0372).

Conclusion: None o f mutant P53, DNA ploidy and HPV 16 showed significant correlation to clinical CR rate, 2 year RFS and 5 year OS. Both of HPV 18 and SPF affect treatment response while only a low SPF predict independently a high CR rate.

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Phase II study of capecitabine (C) in patients with metastatic squamous cell carcinoma of the cervix (SCCC)

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Aim: The efficacy of C correlates with the level of thymidine phosphorylase activity (key enzime of C's metabolism). The highest thymidine phosphorylase activity is registered in SCCC tissue.

Patients and methods: Pts with histological verified metastatic SCCC; measurable disease outside irradiated fields; WHO PS < 2; radiotherapy allowed if finished > 3 months, no more than 2 lines of palliative chemotherapy (CT); adequate liver, renal, hematological functions.

Treatment: Therapy consisted of C 2 500 mg/m2/day, d1- d14, q 3 weeks (1- 8 cycles). Total number of cycles: 72. Median duration of treatment: 7 weeks (min - 3, max - 28).

Results: 25 pts have been accrued; results on 24 pts are available. Pts characteristics: median age 44.6 (25-70); median WHO PS - 1.

Previous treatment: none - 2 pts, radiotherapy - 11 pts, surgery+radiotherapy - 12 pts, CT - 15 pts, CT-naive - 10 pts.

Overall RR - 4/24 pts (17%) (CR-2, PR-2), NC -10/24 pts, PD -10/24 pts. Duration (in months) of CR: 2+ and 7+, of PR: 4+ and 5+; median duration of NC: 2.5. Three of all responsive pts were CT-naive.

All pts were evaluable for toxicity exept 1 (lost for follow-up after 1 cycle). Toxicity included: hand-foot syndrom: G3 - 1/24 pts (1.5% of cycles); G 1-2 - 11/24 pts (43% of cycles); G 1-2 diarrhea: 5/24 pts(7% of cycles); G 1 stomatitis: 4/24 pts(6% of cycles); G 1-2 nausea: 10/24 pts (25% of cycles); G 1-2 asthenia: 12/24 (29% of cycles); G1 dermatitis: 1/24pts (3% of cycles).

Conclusions: C is well tolerated and clinically active cytostatic agent in CT-naive pts with metastatic SCCC.