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Quality of life in patients with cervical cancer during concomitant radio-chemotherapy

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Background: The benefit of radio-chemotherapy with cisplatin in cervical cancer was proved in many studies, the indicated cisplatin schedules remains to be decided. As consequences in Institute of Oncology Cluj-Napoca, in 2003 a randomized phase three trial was initiated, which compares two single-agent cisplatin regimens, one of the aims being the quality of life evaluation.
Material and methods: Between March 2003 and November 2004, this study included 300 patients with cervical cancer stage IIB (143), IIIA (101) and IIIB (56). The patients were randomly assigned in one of the two arms of the protocol: (A) cisplatin 20 mg/m^2 × 5 days, every 21 days (149 patients) and (B) cisplatin 40 mg/m^2/weekly (151 patients), administered concomitant with the radiotherapy. After 46 Gy on the pelvis patients with good response were operated (radical hysterectomy with pelvis lymphadenectomy) and the others continued radio-chemotherapy until 64 Gy. The patients' quality of life from the two arms of the protocol was measured using the European Organization for Research and treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C 30, v.3.0) at randomization and in the 3rd and 5th week during radio-chemotherapy.
Results: The compliance rate at start-line (baseline) was 94%, in the 3rd week 91% and in the 5th week 78%. In arm (A) a significant improvement of global health status ($p < 0.01$) and a decrease in pain ($p < 0.01$) were observed, while in arm (B) fatigue increased ($p = 0.01$) and role functioning diminished ($p = 0.05$). In both treatment arms depress and feel tense (emotional functioning) ($p < 0.01$ and $o = 0.05$)), nausea and vomiting ($p < 0.01$), and diarrhea intensified ($p < 0.01$).
Conclusions: Concomitant radio-chemotherapy with cisplatin = 20 mg/m^2 × 5 days, every 3 weeks offers improved quality of life for patients with cervical cancer. In the future these data are going to be analyzed in comparison with objective results.

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The importance of interval from debulking surgery to the beginning of chemotherapy in ovarian cancer patients

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Background: Ovarian cancer has a poor prognosis, with 5-year survival ranging from 50–85% for early stage tumours (FIGO stages I-II) to 5–20% for advanced stage disease (FIGO stages III-IV). The standard therapy for advanced disease is debulking surgery followed by platinum-based therapy. The timing of chemotherapy initiation after debulking surgery is a matter of concern and patients are often excluded from clinical trials if they cannot commence chemotherapy within 6 weeks of surgery. However, no studies have shown significant differences in survival among patients who received chemotherapy sooner or later after surgery. This work was designed to ascertain whether there is any influence of the interval from surgery to the beginning of chemotherapy on survival in patients with ovarian cancer treated with platinum-based chemotherapy.
Material and methods: We analysed patients from our database. For the last 7 years we have recorded clinical data on all patients coming through the ovarian cancer clinic. Univariate survival analyses were executed using the log-rank test. Multivariate analyses were performed using Cox regression model.
Results: We analysed 525 patients with epithelial ovarian cancer who underwent surgery and post-operative chemotherapy. The mean age of the sample was 57 years old. Most patients (65%) had stage 3 or 4 disease as well as macroscopic disease after debulking surgery (58%). The median follow up was 24 months. We stratified the interval from surgery to chemotherapy in 3 groups: patients who received chemotherapy within 4 weeks from surgery (group 1; $n = 72$), between 4–8 weeks after surgery (group 2; $n = 349$), and more than 8 weeks after surgery (group 3; $n = 102$). In the multivariate analysis we have found no significant statistical differences in survival among the 3 groups. Bulk of residual disease after surgery ($p < 0.0001$), performance status ($p = 0.010$) and post-chemotherapy CA-125 ($p<0.0001$) were independent prognostic variables.
Conclusions: This study suggests that the interval between debulking surgery and beginning of chemotherapy is not an independent prognostic factor for overall survival. It is important to emphasize that we analysed the survival of patients that have started chemotherapy more than 8 weeks after surgery.

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Randomized trials comparing chemotherapy and hormonal therapy regimens for advanced endometrial cancer: biases and evolution over time

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Background: Several chemotherapy and hormonal therapy regimens have been proposed for the treatment of women with advanced endometrial cancer. We systematically evaluated the available data from randomized trials and examined whether there is evidence for any superior efficacy of specific regimens in overall survival or whether biases could be detected in this literature.
Material and Methods: We searched MEDLINE, EMBASE and the COHRANE Library until April of 2005 for randomized controlled trials evaluating various chemotherapy or hormonal therapy regimens in patients with locally advanced or metastatic endometrial cancer. We focused on survival outcomes and examined trial characteristics pertaining to quality and potential biases.
Results: Across 17 eligible trials (3,006 patients randomized in 34 arms), only 4 regimens were involved in more than 1 trial, and only two trials had used the same comparison of regimens. A statistically significant effect in survival was seen only in one recent trial, but it was borderline ($p = 0.032$) and amounted to only 3 months difference in median survival. Only 3 trials (17%) described an appropriate mode of randomization, only 8 (47%) described an appropriate mode of allocation concealment, only 8 (47%) did not clearly violate intention-to-treat and none of the trials were blinded. Median survival was seemingly longer in more recent compared with older trials, but this was entirely attributed to the inclusion of significantly fewer patients with poor performance status in more recent trials.
Conclusion: Randomized trials of systemic treatment in advanced endometrial cancer suffer from fragmentation of research efforts and there is evidence for several biases plaguing their results. Transparent efforts should be made to improve the situation, if any real progress is to be made.

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Outcome after combined modality treatment for uterine papillary serous carcinoma: a rare cancer network (RCN) multicenter study

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Background: There are no established guidelines for treatment of uterine papillary serous carcinoma (UPSC), either in the adjuvant setting or in advanced disease. The aim of this retrospective, multi-center study was to analyze the outcome of patients (pts) with UPSC treated with combined modalities.
Methods: This was a cooperative study within the framework of the RCN. Charts of patients with UPSC diagnosed between 1972 and 2003 were reviewed. Pts were followed for 3–294 months (median 33). Treatment included surgery, chemotherapy, and/or radiation therapy (RT) according to the discretion of the treating physician.
Results: 110 pts, 37–87 yrs old (median 67) were included. Histology features: mixed histology containing UPSC elements and typical adeno-carcinoma was found in 23 pts (21%), pure UPSC in 87 pts (79%). Stage distribution: stage I 43 pts (39%), II 16 pts (15%), III 29 pts (27%), IV 21 pts (19%), no data 1 pt. 103 pts had surgery, 5 pts biopsy only. 62 pts (56%) were treated with RT in an adjuvant setting, 9 pts irradiated for palliation, and 7 for pelvic recurrence. 38 pts (35%) received platinum-based adjuvant chemotherapy (CT). In 41 pts CT was given for persisting disease, resulting in 46% response rate (6 complete and 13 partial responders). 38 pts (35%) are alive and NED, 7 (6%) are alive with disease, 53 (48%) died of disease, 11 (10%) died of other causes, and one died of toxicity.

Five-year disease specific survival (DSS) rates were as follows: All pts (N = 110) 47%, mixed type pathology 78%, pure UPSC 39% (p<0.0064), stage 1&2 72%, stage 3&4 13% (p < 10−6), pts receiving adjuvant CT 48%, no CT 46% (p = 0.82), pts receiving RT 50%, no RT 43% (p = 0.23).
5 yr disease free survival rates were as follows: all pts 42%, mixed type 66%, pure UPSC 36% (p = 0.015), stage 1&2 60%, stage 3&4 15% (p < 10−5), pts receiving CT 35%, no CT 47% (NS), pts receiving RT 53%, no RT 28% (p = 0.016). In a Cox regression analysis for DSS including pathology, stage, adjuvant CT and RT: stage [HR 3.9 (CI 2.1−7.2) p = 0.0001] and pathology subtype [HR 2.4 (CI 1.02−5.9) p = 0.046] highly significant. Adjuvant CT not significant. RT was marginally significant [HR 0.6 (CI 0.3−1.02) p = 0.059]. RT reduced pelvic recurrence rate (p = 0.078).
Conclusions:
1. Stage of disease and pathology subtype are significant prognostic factors.
2. Results do not support any benefit from adjuvant chemotherapy.
3. For radiotherapy a trend of improvement in local control and disease free survival was observed.

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A randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate risk endometrial carcinoma: a Japan Gynecologic Oncology Group study

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Background: Optimal adjuvant therapy for intermediate risk endometrial cancer patients is poorly defined.
Materials and Methods: A Japan Gynecologic Oncology Group conducted a multi-center randomized Phase III trial of pelvic radiotherapy (PRT) vs. cyclophosphamide-doxorubicin-CDDP (CAP) chemotherapy in women with intermediate risk endometrial carcinoma. As eligibility criteria, after initial surgical staging including TAH&BSO with pelvic and/or paaraortic lymphadenectomy, no residual tumor was required. Pathological examination showed >1/2 myometrial invasion, adenocarcinoma with any grade, but without central pathology review. PRT arm employed 50 Gray (Gy) in 20−25 fractions. CAP arm consisted of cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2) and cisplatin (50 mg/m^2) every 4 weeks for 3 or more courses. Study endpoints were progression-free survival (PFS), overall survival (OS), and incidence and types of toxicity.
Results: 475 pts were entered from 1/1994 to 12/2000. but 41 were ineligible due to ⩽ 1/2 myometrial invasion, histology of sarcoma, rapid progression after entry. Because of the different biological behavior of non-endometrioid histology, 49 patients were excluded. Of the 385 evaluable endometrioid adenocarcinoma, 193 were to receive PRT arm and 192, CAP arm. Patient characteristics were mostly well balanced including median age, co-morbidity, and type of hysterectomy. Postsurgical stages were roughly 60% of Ic, 25% of II and IIIa and 10% of IIIc. Tumor grades were G1 55%, G2 30%, and G3 15%. Pelvic lymphnode metastases were 10.9% in PRT arm and 11.5% in CAP arm. Both treatment arms were completed up to 95%. Median total dose was 50 Gy in PRT and 1,309 (c)/120(a)/180(p) mg/m^2 in CAP arm with median 3 courses. Adverse effects were not significantly increased in the CAP arm (4.7%), compared to PRT arm (1.6%) (p = 0.077). Median follow-up was 60.8 months (range 2.2−60.8). Response and Survival: There were no statistically significant differences in PFS and OS between the 2 regimens for all 374 pts. The PFS of PRT and CAP arms was 84.0% and 82.1%, and the OS of PRT and CAP arms was 85.9% and 87.1%, respectively. In a subgroup analysis, among 184 pts with low intermediate risk as stage pTIc (except >70 yo., or G3), the PFS of PRT and CAP arms was 94.3% and 88.6%, and the OS of PRT and CAP arms was 95.0% and 91.7%, respectively. Among 119 pts with high intermediate risk as stage Ic (>70 yo., or G3), II and IIIa (positive cytology), CAP arm significantly improved PFS (p = 0.03) and OS (p = 0.01) when compared with PRT. Recurrence rate in each PRT and CAP arm was 15.1%, 16.5%, respectively, with 30% pelvic and 70% extrapelvic recurrent sites.
Conclusions: Adjuvant cisplatin-based combined chemotherapy might have potential as an alternative to radiotherapy for intermediate risk endometrial cancer, such as stage Ic, II, or IIIa (positive cytology).

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Cytoreductive surgery plus intraperitoneal hyperthermic perfusion in the treatment of recurrent epithelial ovarian cancer

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Background: The optimal salvage therapy for recurrent ovarian carcinoma has not been clearly established. We investigated the effect of an aggressive approach consisting of cytoreductive surgery plus hyperthermic intraperitoneal drug delivery followed by adjuvant systemic chemotherapy.
Patients and methods: 34 patients with recurrent ovarian carcinoma were treated by cytoreductive surgery plus intraperitoneal hyperthermic perfusion. Median patient age was 53 years (range, 30−67) and mean follow-up was 17.4 months (range, 0.3−36.0). All patients had been pretreated by surgery and cisplatin/Taxol-based regimens. The intraperitoneal hyperthermic perfusion was performed with the open Coliseum technique, using a preheated polysaline perfusate containing mitomycin (20 mg/m^2) plus Mitoxantron (20 mg/m^2) through a heart-lung pump (mean flow of 1500 mL/min) for 60 min in the hyperthermic phase (42ºC). At the first 3 post-operative days 5-Fluorouracil 500 mg/m* was applicated intraperitoneally with a dwell time of 23 hours. 3 cycles of adjuvant systemic chemotherapy were given using Topotecan 1.0 mg/m* d1−4 and Gemcitabine 1000 mg/m^2 d1, 8 with a treatment free interval of 14 days.
Results: 37 procedure have been performed in 34 pts. Two-year overall survival was 68% with 80% for pts. with complete cytoreduction (CC0 /1). Median time to progression was 14.5 months. Treatment-related morbidity, 30 days – mortality and acute toxicity (grade III+IV) rates were 10.8%, 0% and 6%, respectively.
Conclusion: Complete cytoreduction plus hyperthermic peritoneal perfusion plus adjuvant chemotherapy seems to be an effective treatment for recurrent ovarian carcinoma. Morbidity and mortality rates are in line with other major oncologic operations.

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Human leukocyte antigen (HLA) a2 as a negative prognostic factor in ovarian cancer patients

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Background: We have shown recently that HLA-A2 frequency and ovarian cancer mortality rates are higher in Scandinavia than in the rest of Europe. Furthermore we could define a selected group of ovarian cancer with high frequency of HLA-A2 phenotype, related to clinical parameters.
Material and methods: A total of 125 patients with epithelial ovarian cancer were recorded by age, histology, stage and treatment. Group 1 included 28 cases of advanced ovarian cancer, which were analyzed for HLA-A, -B, -C and -DRB1 expression by PCR/sequence-specific oligonucleotide hybridization procedure (PCR/SSOP). HLA frequencies from healthy Swedish and other European countries bone marrow donors (Bone Marrow Donors Worldwide, Leiden, The Netherlands) were used as comparison. Group 2 (n = 97) represented patients consecutively admitted at our department during 1995. So far, HLA-A2 PCR/SSOP typing was performed on DNA extracted from paraffin-embedded tissue specimens in 35 patients.
Results: *Group 1:* The HLA-A2 genotype was found in 46% of the patients (healthy Swedish population-35%); among patients with serous adenocarcinomas the frequency was even higher. A3 allele was poorly represented (12% vs. 17%). Seven patients were homozygotes for A2 allele (25%), which is two times the healthy Swedish population (12%), and three times the median frequency in Europe (8%). We also observed an increase in several A2, B and DRB1 haplotypes. Median overall survival among HLA-A2 positive patients was 2.6 years (min 1.5 – max 6.2) versus 3.1 in non-A2 patients (min 1.3 – max 8.7).
Group 2: So far, 35 patients have been tested, and 21 were found positive for HLA-A2 phenotype (60%). Serous adenocarcinomas were found in an excess of A2 positive (67%) vs. 43% of A2 negative patients. After five years, 70% stage I-II and 20% stage III-IV patients were alive. None of the A2 positive patients was alive compared to 50% of the A2 negatives.
Conclusions: Presence of the HLA-A2 allele seems to be correlated with poor prognosis in ovarian cancer patients. HLA-A2 homozygotes and some HLA-A2-B and -DRb1 haplotypes are higher expressed than in healthy individuals. Ongoing investigations are launched to study HLA-A2 as a