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Endometrial carcinoma (EC) in women with breast cancer (BC)

H. Mignotte[1], A. Lesur[2], E. Luporsi[2], J.F. Rodier[3], B. Cutuli[3], S. Lasry[4], L. Mauriac[5], C. Granon[6], C. Kerr[7], S. Giard[8], C. Hill[9], B. De Lafontan[10], C. De Gislain[11], J. D'Anjou[12], E. Fondrinier[13], C. Lefeuvre[14], C. Lasset[1], V. Bonadona[1], F. Chauvin[1]. [1]Centre L Bérard, Lyon; [2,3,4,5,6,7,8,9,10,11,12,13,14]Fédération Nationale des Centres de Lutte contre le Cancer, France

Methods: A multicentre, hospital-based, case-control study, was organized in 14 French cancer centres, comprising 138 women in whom an EC had been diagnosed between 1976 and 1990, at least 6 months after BC. A total of 467 women with BC were individually matched on date of birth and date of diagnosis of BC.

Results: In a multivariate analysis, the risk of EC was significantly increased with use of TAM (mOR = 4, p = 0.0014), length of treatment more than 3 years (mOR = 3.9, p = 0.016) and pelvic radiotherapy (mOR = 3.2, p = 0.006). TAM has been taken by 91 cases and 191 controls. Women with EC occurring after completion of TAM were younger at time of BC diagnosis than those observed on untreated women or with EC during TAM (Median age: 50 y. VS 63 y and 61 y: p = 0.01.). The median cumulative dose of TAM was not significantly different between the two exposed groups nor the median duration of exposure. Women who had endometrial carcinoma after TAM therapy were younger at BC diagnosis, underwent more frequently pelvic radiotherapy and showed more advanced stages and poorer pronosis. Median follow-up after EC was respectively 40 m. and 84 m. for treated and untreated women. The overall survival (OS) after EC was shorter for the TAM treated group than for untreated women (p = 0.005) and survival was better for EC observed during TAM therapy than for those diagnosed after ended treatment p = 0.02.).

Hypothesis: EC observed during TAM therapy could be prevalent neoplasia but an hypothetical oncogenic effect of TAM and/or pelvic radiotherapy could be discussed for EC observed after treatment ended.

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Acute and late toxicity in the adjuvant radiotherapy of endometrial carcinoma. Analysis of 215 patients

J.F. Perez-Regadera, M.T. Murillo, S. Sancho, G. Sanchez-Rodillo, M.J. Guereña, R. Prados, B. Ludeña, M.A. Cabeza, C. Carpio, A. Bartolome, E. Lanzos. *Department of Radiation Oncology, University Hospital "12 de Octubre", Madrid, Spain*

Purpose: To evaluate the acute and late toxicity in the adjuvant radiotherapy treatment of endometrial carcinoma and its influence in the outcome and the quality of life in the patients that underwent a pelvic irradiation.

Methods: From 1978 to 1995, 215 patients were diagnosed of endometrial carcinoma in stage I and II, previously treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) or TAH-BSO and sample of pelvic nodes (TAH-BSO-SL). 168 patients were treated with TAH-BSO and 47 with TAH-BSO-SL and subsequently treated with external radiotherapy exclusively (18 patients), external radiotherapy and intracavitary insertion (180 patients) or intracavitary insertion exclusively (17 patients). To evaluate the toxicity we used the RTOG classification.

Results: Acute toxicity was observed in 161 patients (74.9%). It was G1 in 26.5%, G2 in 35.8, G3 in 11.2% and G4 in 1.4%. The more frequent symptoms were diarrhea (N = 116), dermatitis (N = 60) and cystitis (N = 32). An interruption of the treatment was necessary in 56 patients because of the acute toxicity. The local control was decreased in the group of patients in which the treatment was extended more than seven weeks (p = 0.002). Late toxicity was found in 45 patients (21%). It was G1–G2 in 35 patients (16.3%) and G3–G4 in 10 patients (4.7%).

Conclusion: An inadequate control of acute symptoms during pelvic irradiation influence in the local control and survival in patients with endometrial carcinoma.

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Radiation therapy for primary vaginal cancers

G. Hänsgen. *Dept. of Radiotherapy, Martin-Luther-University Halle-Wittenberg, Germany*

Purpose: We have retrospectively evaluated the treatment results of radiotherapy for vaginal carcinomas.

Methods: From 1980 through 1991, 97 patients (median age 68 years) were treated for vaginal cancers, 79 had squamous cell carcinomas. All of them received HDR-brachytherapy. 45 had additional external megavoltage radiotherapy with curative intent, the other were treated with brachytherapy alone or in combination with orthovolt with palliative intent because of advanced disease or poor general condition.

Results: The 5-year survival after combined brachy- plus external radiotherapy was 85% (6/7) in stage I, 80% (12/15) in stage II and 35% (6/17) in stage III. In the brachytherapy alone group, 43% (9/21) in stage I and 29% (5/17) in stage II survived 5 years. 8/45 (17%) of patients with external megavoltage therapy developed local recurrences as compared to 26/53 (49%) without adequate external radiotherapy. Vaginal fistulas occurred in 3 patients.

Conclusions: Combined HDR-brachytherapy plus external radiotherapy yields good local control and survival figures in vaginal cancers at an acceptable low rate of complications.

928 ORAL

Isolated local recurrence in carcinoma of the vulva: Prognosis and implications for treatment

C. Faul[1], D. Miramow[2], K. Gerszten[1], C. Haung[3], R. Edwards[4]. [1]Department of Radiation Oncology; [2]Department of Pathology; [3]Department of Statistics; [4]Department of Gynecologic Oncology, Magee-Womens Hospital, University of Pittsburgh, Pittsburgh, PA, USA

Purpose: Despite a lack of published data, an isolated vulvar recurrence is regarded as having a high surgical salvage rate when compared to regional or distant recurrence. This study evaluates the impact of local recurrence on survival.

Methods: Forty-seven of 310 patients were found to have an isolated vulvar recurrence following definitive therapy for squamous cell carcinoma between 1980–96 at a single institution. Actuarial survival rates were calculated by the Kaplan-Meir method and prognostic factors analyzed by the Cox proportional hazards model.

Results: Thirty-one patients were treated with surgery alone, 14 with combined therapy or radiation alone and 2 were not treated. Actuarial 5 year survival was 45% for all patients with no significant difference between the treatment groups. On univariate analysis disease free interval <1 year, clinical stage, pathologically positive groin nodes at presentation, capillary space involvement (cls), and size of recurrence were all significant prognostic factors for survival. On multivariate analysis, only cls, tumor size at recurrence and pathologically positive groin nodes reached statistical significance. When grouped, patients with a tumor <3 cm at recurrence, negative cls and pathologically negative groin nodes had an actuarial 2 year survival of 60% compared with 30% for patients with >3 cm tumor, positive cls and pathologically positive nodes. The majority of patients died of either uncontrolled loco-regional disease (9) or distant disease (13).

Conclusion: An isolated local recurrence is a poor prognostic factor for survival in carcinoma of the vulva. As this group of patients have a high local and distant failure rate, more innovative treatment strategies are needed, such as using systemic therapy in combination with better local treatment.

929 ORAL

Radiotherapy and hyperthermia in inoperable pelvic tumours: Results of Dutch randomized studies

J. van der Zee[1], D. González González[2]. [1]University Hospital/Dr. Daniel den Hoed Cancer Center, Rotterdam; [2]Academisch Medisch Centrum, Amsterdam, The Netherlands

Introduction: Advanced, inoperable tumours originating from the bladder, cervix, and rectum are characterised by disappointing local control rates following radiotherapy. Both preclinical and clinical data have shown that the efficacy of radiotherapy can be improved by the addition of hyperthermia.

Methods: The effect of hyperthermia in addition to standard radiotherapy has been investigated in a randomized study, including patients with bladder (T3 and T4), cervical (IIB-distal, IIIB and IV), and rectal (primary or recurrent) cancer.

Results: The preliminary results including total 298 patients show a significant improvement in complete response rate by additional hyperthermia, from 37% to 58%, for the whole patient group. The effect of HT was most impressive in the group with cervical cancer, with significant improvement of both local control and overall survival. In bladder cancer, the improvement in local control was temporary and not resulting in a better survival. In rectal cancer, the improvement in local control seemed less and was not

significant. The available data show no indication for enhanced radiation toxicity.

Conclusions: It was concluded to offer combined treatment standard to patients with tumours of the uterine cervix, and to develop new study protocols for patients with bladder and rectal cancer.

930 ORAL

Phase II multicentric trial of neoadjuvant bleomycin, ifosfamide and carboplatin (BIC) in locally advanced cervical cancer

A.M. Murad, S.A. Triginelli, R.C. Guimarães, B.C. Aragão, O.X. Gonçalves, L.C. Lima. *Oncology Department, Hospital das Clínicas, Universidade Federal de Minas Gerais e CEPON, Florianópolis, SC, Brazil*

Purpose: Based upon the very good results in terms of objective response (OR) and paliation with the use of BIC protocol in the treatment of patients with advanced cervical cancer (Murad et al J Clin Oncol 12: 55–59, 1994) besides the inadequate results obtained by neoadjuvant chemotherapy (CT) and radiotherapy (XRT) in this setting, we started this prospective trial in April, 1994, aiming to determine the efficacy of neoadjuvant BIC before radical surgery in previously untreated patients with locally advanced squamous cell carcinoma of the cervix.

Methods: Patients with stage IIB, III and IVA, CT and XRT naive, were assigned to receive 30 mg of B i.v. bolus on day 1; 200 mg/m2 of C i.v. on day 1; and 2 g/m2 of I in a 2 hour i.v. infusion days 1–3. The cycles are repeated every 28 days on an outpatient basis. After 3 cycles, if OR is confirmed by clinical/radiological evaluation the patient receive one more cycle of BIC and then go to surgery (radical hysterectomy). Only patients with positive linphnodes or positive surgical resection margins receive consolidation XRT. Stable and progressive disease are treated with standard XRT.

Results: Up to now 24 patients were accrued. 3 refused surgery after CT, although attaining OR. 20 are now eligible for response assessment: stage IIB barrel shaped: 2 (10%), IIIA: 1 (10%), IIIB: 14 (70%), IVA: 5 (25%). Response after CT: OR-4 (70%) (95%CI:49%–90%); CR-5 (25%) and PR-9 (45%). All 14 responders went to surgery: 12 (60%) attained substantial tumor regression and had a potentially curative surgery. One patient attained CR pathologically documented: no tumor was found in the surgical specimen. In 2, stable or unressectable disease were documented. Only 3 patients received consolidation XRT. The median recurrence-free survival has not been reached so far. The 34 month recurrence-free survival is 50%. Almost all patients had nausea and WHO G3 alopecia. Anemia G1 were documented in 28 (37%) cycles, G2 in 6 (8%) and G3 in 4 (5%); leukopenia G1 in 8 (10%) and G3 in 1 (1.3%); thrombocytopenia G1 in 1 (1.3%), henaturia G2 in 2 (2.6%); vomiting G2 in 24 (32%), G3 in 2 (2.6%); infection G1 in 2 (2.6%. No death or G4 toxicity were observed.

Conclusion: These preliminary data are very exciting and promising, suggesting that 60% of the patients with locally advanced cervical cancer can have a potentially curable surgery after primary BIC CT, with a very acceptable toxicity profile. Accrual onto this study continues.

931 POSTER*

Postoperative radiotherapy for cervical carcinoma stage Ib and IIa with positive iliacal lymph nodes; A national case-study

H.A. van den Berg, M.J.J. Olofsen-van Acht, J.P.C. van Santvoort, M. Seven, S. Quint, P.C. Levendag. *Dept. of Radiation Oncology, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*

Purpose: To assess the variation in treatment portals for postoperative radiotherapy for stage Ib and IIa N+ cervical carcinoma.

Methods: Radiation Oncologists (RO; n = 17) from all Radiotherapy Institutes in The Netherlands were asked to delineate treatment portals on a lateral and anterior simulation film in case of radiotherapy following a radical hysterectomy with lymphnode dissection for stage Ib and IIa cervical carcinoma with positive iliacal lymph nodes. They also depicted the clinical target volume (CTV). A planning target volume (PTV), using 47 normal lymphangiograms and CT-data of the pelvis of 15 patients was defined. Subsequently all simulation films of the 17 RO were digitized and planned and evaluated for adequacy in covering the reference PTV.

Results: Major variations were observed in shapes and sizes of the portals and the used treatment techniques. In 31% of the cases the PTV was not irradiated according to their own dose prescriptions. Twenty-five percent of the treatment plans did not cover the PTV at the lateral borders of the parametria in the AP direction, assuming a margin of 5 mm or more between PTV and field border.

Conclusions: In this study there appears to be no consensus on the areas to be irradiated. Also, if the defined PTV, based on lymphangiograms and CT-data, is taken as a reference, in 25% of the cases the PTV was inadequately covered.

932 POSTER

Expression of cripto-1, a new ligand of the EGF superfamily, in gynecological carcinomas

A. Ebert[1], J. Reinhold[1], J. Stieler[1], W. Pritze[1], D.S. Salomon[2], H. Weitzel[1], G. Schaller[1], R. Brandt[3]. [1]*Free University Berlin, Medical Center Benjamin Franklin, Department of OB/GYN, Germany;* [2]*National Cancer Institute, LTBI, Growth Factor Section, Bethesda, USA;* [3]*Dept. CDD Technology, Ciba-Geigy AG, Basel, Switzerland*

Purpose: The expression of CR-1 was analyzed on the background of clinical staging and grading in endometrium, ovarian and cervical cancers.

Methods: The expression of CR-1 was examined by immunohistochemistry in paraffin-embedded tumor tissue samples from 25 patients with endometrial cancer (EC), 25 with cervical carcinomas (CC) and 31 with ovarian cancer (OC). A high protein specific polyclonal Ab against human Cripto, the APAAP staining method and a immunreactive score (IRS) were used.

Results: 60% of EC, 71% of OC and 72% of squamous CC expressed CR-1. The expression was not stage dependent. Most of G2 ECs (85.7%) expressed CR-1. A positive correlation between the expression of CR-1 and the grading seems to be possible in CC. CR-1 was significantly overexpressed in G2 tumors (92.3%) than in G3 tumors (36.4%). In OC, G3 tumors (78.6%) expressed significantly more CR-1 than G2 tumors (64.3%)

Conclusions: Previous studies have shown that CR-1 is overexpressed in many colorectal, gastric, breast, ovarian and pancreatic malignancies. In the present study about 70% of the common gynecological carcinomas were CR-1-positive. CR-1 seems to be a new interesting factor with clinical relevance (prognostic value, LN spreading, tumor biology) in gynecological oncology.

933 POSTER

Efficacy of supplementary treatment with isotretinoin combined with interferon-alpha-2a in primary radiotherapy of cervical cancer – Results of a clinical phase-II-study

U. Köhler[1], G. Füchsel[2], G. Hänsgen[3]. [1]*Department of Gynecology, University of Leipzig;* [2]*Department of Gynecology;* [3]*Department of Radiotherapy, Martin-Luther-University Halle, Germany*

Purpose: Irresectable cervix cancer (stage FIGO IIb–IIIb) is normally treated with combined radiotherapy (percutaneous/afterloding). Several previous in-vivo- and in-vitro tnals suggest an improvement of radiosensitivity by adding retinoids and interferon-alpha in squamous cell cervical cancer.

Methods: In a pilot study three different departments of two university-hospitals recruited 33 women (34–84 years) with SCCC (stage IIb–IIIb) within 9 months. All women received 6 Mio I.U. Interferon-alpha-2a (Roferon ®) s.c./daily and 1 mg/kg/bw Isotretinoin (Roaccutan ®) p.o./d for 12 days prior to radiotherapy. During radiotherapy all dosages were decreased, to prevent toxic side effects:

Interferon 3 Mio I.U. three times weekly s.c. and Isotretinoin 0.5 mg p.o. daily were administered until the maximum dosage of irradiation was reached (52–54 Gy). All patients were treated successfully.

Results: Preliminary data are as follows: 29 patients were totally evaluated, 4 patients are under therapy or evaluation.

CR occurred in 26 patients, PR in 3 patients. Almost all patients tolerated the treatment well, toxicity was mild (flu-like symptoms, skin dryness, reversible elevated liver enzymes, increased tumor vulnerability). WHO-Grade IV side effects were not observed. Long-term effects cannot be stated yet.

Conclusion: Further analysis (i.e. follow-up and randomized regimens in future) is necessary.