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PELVIC EXENTERATION AS SURGICAL TREATMENT OF LOCOREGIONALLY RECURRENT CERVICAL CARCINOMA

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When a locoregional recurrence of a cervical carcinoma occurs, the last hope from a curative surgical enterprise may be a pelvic exenteration. This procedure remains exceptional. Technically, it combines several standard resections of a number of pelvic organs, such as hysterectomy or colpectomy, partial or total cystectomy, perineectomy, bowel resections, lymphadenectomy.... But its specific application to each of these pelvectomies depends on the optimal process accorded to each particular patient, thereby strongly contrasting with the very codified treatment of initial disease. Using data from a historical series of 30 cases and the material from recent literature, we will try to define the reasonable frontiers to be maintained while undertaking the association of necessarily wide resections along with ambitious functional repairs (such as urinary and digestive continuity, conservation of sphyncteral control, vaginal replacement, filling of large pelvic losses ...). The goal is a far from prohibitive 5 year-survival, from 15% globally to 50% in some rigorously selected series. Some mediocre results emphasize the need for evaluation of pejorative criteria, such as age, lateropelvic or upper urinary extensions, lymph node metastasis, or a short delay between initial treatment and relapse. Nevertheless, and however dramatic these conditions may turn out to be, some palliative indications can still be discussed: indeed, the outcome of a well-done exenteration may be considered less intolerable than unavoidable mechanical complications due to the cancerous propagation in itself.

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ADVANCES IN THE TREATMENT OF LOCOREGIONALLY RECURRENT CERVICAL CANCER

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Whereas 25–50% of selected patients with cervical cancers relapsing centrally in an irradiated pelvis can be salvaged by exenteration, post-irradiation recurrences infiltrating the pelvic side wall have been generally fatal. We have designed the Combined Operative and Radiotherapeutic Treatment (CORT) for local control of post-irradiation recurrences infiltrating the pelvic wall and developed several new surgical techniques for its realization. The aim of the surgical part is (i) the total resection of the tumor with only a microscopic (R1) margin at the pelvic wall preserving the bony pelvis and the neurovascular support of the leg, (ii) the modulation of the therapeutic index for a second high-dose irradiation of the pelvic wall by transferring autologous tissue from the abdomen or the thigh, (iii) the reconstruction of pelvic organ functions lost due to the tumor resection. The tumor bed is irradiated postoperatively with brachytherapy through transcutaneous guide tubes implanted at the pelvic wall. From 4/1989 until 12/1994 we have treated 48 patients with post-irradiation recurrent or persistent gynecologic malignancies infiltrating the pelvic wall with CORT. At a median follow-up of 33 months (range 3–71 months) the five-year survival probability calculated with the Kaplan–Meier method was 44%. Censored severe complication rate at five years was 33%, no patient died as a consequence of the treatment. Quality of life self-assessed by 15 accessible patients without evidence of disease with a validated questionnaire was rated with 74% of the maximum score points in total.

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CAN WE IMPROVE THE RADIOTHERAPY OF CERVIX CARCINOMA?

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The treatment of advanced cancer of the cervix by radical radiotherapy has, for many decades, utilised very standard techniques of pelvic external beam therapy and intracavitary therapy in which dosage has been dictated by the standard volumes irradiated and normal tissue tolerances to intracavitary brachytherapy. The effect has been that although there has been some difference in outcome between centres in different countries the overall results have remained disappointingly but predictably stable. Three developments offer some long term hope of individual improvements. (1) Pre-treatment imaging—particularly with magnetic resonance scanning. (2) Collimation of the radiation beam based on improved imaging, and most excitingly (3) individualisation of radiotherapy based on *in vitro* assessment of tumour and normal tissue radiosensitivity. Utilising fresh tumour tissue and normal lymphocytes obtained from patients prior to radical radiotherapy the *in vitro* radiosensitivity has been assessed by measuring the surviving fraction at 2 Gy.

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NEOADJUVANT CHEMOTHERAPY (NACT) IN CERVICAL CANCER (CC)

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There are several reasons why the use of NACT in patients (pts) with CC could be an attractive approach, ie uncompromized blood supply to the tumor, enhanced tolerance to CT by the pts, chemodebulking might improve effectiveness of local radiotherapy (RT) and facilitate operability, the possibility of eradication of subclinical metastases and theoretically a higher chemosensitivity of the tumor before surgery or RT. There are a number of phase II reports on NACT, which although not definitive, are of considerable interest both in terms of feasibility and (high) response rate. Nearly all regimens used in this setting included the single most active cytotoxic agent for this disease, cisplatin. Unfortunately, results of randomized trials comparing such NACT regimens followed by RT vs RT alone in pts with locally advanced CC, i.e. stages III and IVA, tended to be disappointing. Complete response rates were generally low, and local failure rates were not necessarily decreased, possibly reflecting cross-resistance between drugs and irradiation. Long-term survival benefit is unclear, but sometimes even worse than with RT alone. Data on NACT followed by surgery, in particular for pts with bulky stages IB-II disease seem more promising. Complete response rate in these circumstances tends to be higher, but is dependent on the number of cycles given. Available studies suggest a decreased incidence of positive lymph nodes found at surgery after NACT compared with historical controls. Although the NACT/surgery approach seems to be of interest, randomized trials with adequate number of pts should be started and mature results of ongoing randomized trials should be awaited before a definitive answer of the influence on survival can be given. None of these approaches can be considered standard care at the present time.

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ASSOCIATION OF 13-CIS-RETINOIC ACID (13CRA) AND ALPHA-INTERFERON-2A (IFN- α 2A) IN MODERATE-SEVERE CERVICAL INTRAEPITHELIAL NEOPLASIA

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Recent studies both *in vitro* and *in vivo* have suggested a possible synergism between IFN- α 2a and 13cRA. The specific aim of our study was to evaluate efficacy and toxicity of the association of these two agents in patients (pts) with CIN II and III. 13cRA (orally at 0.5–1 mg/kg/day) and IFN- α 2a (i.m. at 3 millions I.U.) were administered simultaneously for 8 consecutive weeks. 22 pts (aged 25 to 58 years), of which 14 CIN II and 8 CIN III, entered the study. 14/22 (64%) histologically verified OR (7 CR and 7 PR were achieved). In addition, 8 SD were recorded. Compliance was generally good and no delays due to toxicity were recorded.

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GENES CODING FOR TUMOR REJECTION ANTIGENS

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We have isolated a number of genes that code for antigens recognized on human melanomas by autologous cytolytic T cells (CTL). A gene named MAGE-1 codes for two different antigenic peptides that are recognized by CTL on MHC molecules HLA-A1 and HLA-Cw16 respectively. This gene belongs to a family of 12 closely related genes. No expression of these genes was found on a large panel of normal tissues

except for testis. The genes of the MAGE family are all located on the q terminal region of the X chromosome. The putative proteins produced by these genes present almost identical hydrophobicity patterns, suggesting that they exert the same function, but this function remains unknown. Gene MAGE-4 carries at least eight alternative first exons preceded by different promoters. The MAGE gene family may therefore ensure that the same function is placed under the control of nineteen different promoters, allowing for very specific spatial and temporal regulation. Gene MAGE-3 codes for a second antigen presented by HLA-A1. The relevant antigenic peptide is encoded by the MAGE-3 sequence that is homologous to the MAGE-1 sequence that also codes for an antigen presented by HLA-A1. Recently, another peptide that is encoded by MAGE-3 and binds to HLA-A2 has been found to be recognized by CTL. Two additional genes that code for tumor antigens and are expressed only in tumors and in testis have been isolated. These genes, named BAGE and GAGE, are unrelated to each other and to the

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IMMUNOTHERAPY WITH AUTOLOGOUS, IRRADIATED MELANOMA CELLS TRANSDUCED WITH THE GM-CSF GENE

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Irradiated melanoma cells, that are transduced with the GM-CSF gene, produce GM-CSF for about one week. The local production of high levels of GM-CSF could attract and stimulate antigen presenting cells, such as dendritic cells, which can present the melanoma associated antigens to cytotoxic T cells (CTLs). In a murine model vaccination with irradiated, GM-CSF transduced B16 melanoma cells protected against challenge with wild type melanoma cells. Based on these data, we are conducting a phase I trial in melanoma patients with advanced disease. Autologous melanoma cells are cultured and transduced with the GM-