945 PUBLICATION

## Modified partial hyperfractionation in radiotherapy for bulky uterine cervical cancer: Reduction of overall treatment time

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**Purpose:** FIGO stage, bulk of disease within each stage, Kamofsky performance status, age, the use of intracavitary radiation, and paracentral dose are accepted as the independent factors of prognosis and outcome in the cure of cervical cancers with radiation therapy. The concurrent boost or accelerated hyperfractionation scheme to reduce the overall treatment time (OT) is not feasible in cervical cancer because of bowel complication unlike the head/neck cancers. In order to improve the local control rate in bulky cervical cancers, we designed non-randomized clinical trial in attempt to find feasibility and toxicity of modified partial hyperfractionation of external beam radiation that could reduce OT by 1 week.

**Methods:** Thirty-one patients (Group 1) with bulky cervical cancer (≈4 cm with stage II and III, ≈5 cm with stage Ib2) entered BID protocol between September 1994 and December 1996 (18 Gy/10 fx in 2 weeks followed by 18 Gy/12 fx, bid in 6 days, then midline block at 36 Gy with 45 Gy to the whole pelvis and 51–59 Gy to the parametrium). The patients underwent high dose rate brachytherapy with 4 Gy/fx × 7 to point A, biw. During the same period, patients with non-bulky tumor (Group 2, n = 31) received conventional treatment and similar brachytherapy.

**Results:** All patients were followed minimum 2 years. The OT was 7 weeks or less in 61.3%, 7.1 to 8 weeks in 29% and more than 8 weeks in 9.7% (19.4%, 51.6%, and 29% in Group 2, respectively, p = 0.003). In both groups, the major reason for treatment interruption was frequent holidays over 3 days. During the treatment, patients in Group 1 tolerated treatments well without excessive side effects and unnecessary treatment breaks even in old age group beyond 65 years old. However, the late rectal complication (rectal bleeding) in Group 1 was frequent (4/31 vs 0) but was self limited within 3–6 months except one patient. Local failure rate at 4 years was 16% and 13% in Group 1 and 2, respectively. Overall actuarial survival rates at 4 years in both groups were 87.1%.

**Conclusions:** Partial Hyperfractionation on 3rd week of radiation permitted the patients to finish their treatment with shorter OT, without excessive acute side effects and with acceptable grade 2 late rectal complications. This treatment scheme could be an effective method in improvement of local control of bulky cervical cancer.

946 PUBLICATION

## Change of proliferative activity and cyclin E expression during radiotherapy in locally advanced cervical cancer

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**Purpose:** Some studies have described decreased pelvic tumor control and survival rates in locally advanced cervical cancer when the overall treatment time in a course of definitive irradiation is prolonged. Fowler emphasized the importance of rapid proliferation of malignant cells that influence tumor control probability. In this study, we investigated changes in Mib-1, PCNA, and cyclin E indices before and during the radiation treatment to clarify the effects of fractionated radiation on the cell cycle and its underlying mechanism.

**Materials and Methods:** Five patients with locally advanced cervical cancer were available for the study. All specimens were excised from tumor tissues before and during radiation treatment (day 0, 8, 15, 22 and 29). Slides were prepared for immunostaining with Mib-1, PCNA and cyclin E monoclonal antibodies. One pathologist counted malignant cell numbers (positive or negative with stain) on 400× color photographs.

**Results:** Mib-1 and PCNA indices were much higher in untreated specimens comparing to cyclin E index. PCNA index was rapidly decreasing with increased radiation dose but Cyclin E index was still high even at 22nd day of treatment. Mib-1 index of 8th day specimen was shown different pattern with patients and since 15th day, there was decreased. There was no recognized tumor cells at 29th day of treatment.

**Conclusion:** This is a study with a small number of patients. But Mib-1 and PCNA were strongly positive even later part of treatment. We will include more patients to analyse the relationship between tumor response and cell kinetics change.

947 PUBLICATION

## Endometrial carcinomas: Prognostic factor in I–II stage

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**Purpose:** To evaluate prognostic factors in patients with stage I–II endometrial carcinoma treated with surgery plus adjuvant radiotherapy (EBRT, EBRT + LDR-BRT, LDR – BRT alone)

**Material and Methods:** From 1/85 to 12/96, 152 patients were admitted in this study (Ib 37%, Ic 39%, IIa 11%, IIb 13%). RT was performed using box technique on pelvis, Rx 18 Mv, personalised blocks, prescribing 1.8–2 Gy at the minimal isodose around the CTV. Total doses ranged within 46–50.4 Gy. In 71 pts a boost was performed with LDR brachytherapy on the vaginal cuff, doses ranged within 10–20 Gy at 0.5 cm from the applicator surface. Brachytherapy was performed in pts with high risk of local relapses, not only for the well-known prognostic factors, but also for the operative technique or surgical complications. 18 pts received only brachytherapy as adjuvant treatment for critical general conditions.

**Results:** No grade III–IV WHO toxicities or complications were seen. With a minimal 2 years follow up, we have observed 9 local and 18 distant relapses. Overall 5 years survival is 78% and NED survival 84%. No significative differences were observed among the three groups of postoperative RT (EBRT, EBRT + BRT, BRT alone). Most important prognostic factor in our series is the tumor volume with a difference (small volume 91 pts, NED survival 90% vs 73% in 61 with big volume; p = 0.03). Other factors show only a trend or no significance.

**Discussion:** In our series adjuvant radiotherapy seems to reduce the incidence local relapses also in high-risk patients. These data invite us to confirm our treatment policy in performing RT, especially delivering local high doses with use of BRT without increase of acute or late toxicities.

948 PUBLICATION

## Comparison of different polymerase chain reaction methods for detection of human papillomaviruses

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**Purpose:** Many epidemiologic studies and basic research on molecular level strongly support the role of human papillomaviruses as etiologic agents in cervical carcinogenesis. There are more than 70 HPV types of which more than 30 infect genital sites and have different oncogenic potential. Diagnosis of HPV infections is of extreme importance in the prevention of cervical cancer.

**Methods:** We tested the presence of HPV DNA by polymerase chain reaction (PCR) in cervical scrapes obtained from consenting women with cytomorphologically abnormal cervical smears. In order to evaluate different PCR approaches for screening and detection of HPVs we used and then compared the results obtained with three sets of general primers localised within the L1 region of HPV genome (MY09/MY 11, inosine-containing MY09/MY11 and L1C1/L1C2) on 164 samples. These results have also been compared with results obtained with type-specific primer pairs for HPV types 6, 11, 16, 18, 31 and 33.

**Results:** HPV DNA was detected in 125/164 (76.22%) cervical scrapes (positive result with at least one set of consensus primers); the concordance of results obtained with three sets of general primers (either positive or negative result) was 53.05%. HPV type was determined in 97/164 (59.15%) samples; in 16/164 (10.37%) samples a multiple HPV infection was found.

**Conclusion:** Simultaneous use of MY09/MY11 and L1C1/L1C2 primer sets in combination with type specific PCR is a valuable method for HPV screening and typing.

949 PUBLICATION

## The association of human papillomavirus, cytomegalovirus and herpes simplex virus infection in human cervical cancer in Taiwan, R.O.C.

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**Introduction:** Human Papillomavirus (HPV) has been suggested to play an important role in cervical carcinogenesis. However, herpes simplex virus

(HSV), cytomegalovirus (CMV) which have been incriminated with varying degree of evidence.

**Materials and Methods:** In 43 surgical specimens of cervical cancer, using PCR, HPV, HSV and CMV were identified by the presence of these viral specific gene fragments. The first pair of consensus primers on L1 region-L1C1 (sense strand) 5'-CGTAAACGTTTTCCCTATTTTTTT (antisense strand) 5'-TACCTAAATACTCTGTATTG were used to detect HPV. The length of this product was 250 bp. To detect HSV DNA, a second pair of primers that bracket a 92 bp segment were used. Their sequences are as follows: 5'-CATCACCGACCCGGAGAGGGAC and 5'-GGGCCAGGCGCTTGTTGGTGGA. These are regions which are identified in the genome of HSV type 1 and 2 and thus do not discriminate between these two types. The third pair primers 5'-TCCTCCTGCAGTTCGGCTTC and 5'-TTTCATGATATTGCGCACCT were used to detect CMV DNA sequence. The length of the PCR product was 240 bp.

**Results:** The prevalence of HPV, CMV and HSV infections was 72%, 67% and 76%, respectively. To examine mutual relationships between HPV with CMV, or with HSV infections. We calculate odds ratio (ORs) with their 95% confidence intervals (95% CI). We found more patients with HPV infections (69.7%) were coinfected with CMV than those without HPV infections (55.6%), with ORs of 2.2 (95% CI 0.40–11.88). Patients with HPV infections (72.7%) were less likely to be coinfected with HSV than those without HPV infections (88.9%) with an ORs of 0.28 (95% CI 0.01–2.69). The proportions of patients with large cell keratinization were 31.2%, 33.3% and 37.5% for those infected with HPV, CMV and HSV, respectively. The correlation between HSV infections and clinical stages were marginally significant, while both HPV and CMV infections were not.

**Conclusion:** This study demonstrated mixed infections of HPV, CMV and HSV in cervical cancer patients, suggesting that CMV and HSV might be cofactors in the malignancy of uterine cervix. Our results indicate that HSV infection associates with the cellular keratinization pattern and clinical stages of squamous cell carcinoma of uterine cervix.

950 PUBLICATION

## Identification of a 100-kb region of common allelic loss on chromosome bands 10q25-q26 in human endometrial cancer

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**Purpose:** Endometrial cancer is one of the common female pelvic malignancies. Incidence of this disease has been doubled in the last decade in Japan. However, molecular mechanisms of this disease are still elucidative. We screened genetic alterations in endometrial cancers by means of CGH, FISH, and microsatellite analysis, and found frequent allelic loss in chromosome 10q.

**Results:** PTEN was recently cloned and mapped on 10q. We analyzed mutation of this gene and found frequent somatic mutations in endometrial cancers. However, our LOH analysis revealed an existence of another region of frequent allelic loss in 10q25-q26, flanked by D10S587 and D10S1723. We have constructed a cosmid and BAC contig of this region, and further studied allelic loss by FISH utilizing these cosmid clones.

**Conclusion:** Finally, we found that three overlapping cosmid clones completely covered the region of common allelic loss, it was included in one BAC clone, the size was estimated to be less than 100-kb. Moreover, there was a cluster of the so-called rare cutters; NotI, MluI, SmaI, and XhoI. Our results suggested a possible existence of the tumor suppressor gene in this region.

951 PUBLICATION

## Adjuvant radiation therapy in the treatment of endometrial stromal sarcoma (ESS)

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**Purpose:** The efficacy of adjuvant radiation therapy in the treatment of ESS has not been clarified.

**Methods:** During 1981–1998, 21 patients with ESS were treated. The age of patients ranged between 44–76 years. The 1989 FIGO classification for endometrial carcinoma was used for reclassification: 11 patients (52.4%) presented in stage I, 1 (4.8%) in stage II, 5 (23.8%) in stage III, 2 (9.5%) in stage IV, and 2 (9.5%) with large tumor relapses. 14 patients (66.7%) presented with a grade 1 tumor, 2 (9.5%) with a grade 2 tumor, 2 (9.5%) with a grade 1 tumor, and in 3 patients (14.3%) tumor grading was unknown. 15 patients (71.4%) were referred for postoperative radiotherapy after hysterectomy, 2 for primary radiotherapy and 4 for radiotherapy with a palliative intention. 20 patients received external beam therapy in daily fractions up to a mean dose of 47.9 (27–57) Gy to the pelvis. 17 patients (81.0%) received brachytherapy to the vaginal vault.

**Results:** The mean follow up was 70.3 (8–170) months. 11 patients are still alive, 10 without tumor and 1 with tumor. 10 patients are dead, 6 due to ESS, 1 due to breast cancer, and 3 due to intercurrent disease. After adjuvant radiotherapy 3 patients (20%) with grade 3 tumors had tumor recurrences. All had distant metastases, one had local failure additionally. The patients with primary treatment died after a mean time of 8.5 months due to intercurrent diseases. All patients with a palliative intention showed partial response. 3 patients died due to tumor, and one patient with a grade 1 tumor is still alive 12 months after treatment.

**Conclusion:** Adjuvant radiation therapy is an effective treatment for patients with ESS due to the increase of local control and the increase of disease specific survival in early stages.

952 PUBLICATION

## Vulvo-vaginal reconstruction in advanced oncologic pathology

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**Introduction:** Ablative surgery of advanced pelvic primary tumours or of its recurrences revolving extensive excisions represents a great reconstructive challenge, in which the main goals are to minimise complications and to find a better quality of life to patients.

To provide these reconstructions one need an appreciable amount of tissues, which is only possible to obtain using myocutaneous flaps. The two most used options are the Rectus Abdominis and the Gracilis flaps.

**Patients and Methods:** Between March 1994 and December 1998, we performed vulvo-vaginal reconstructions with Gracilis myocutanous flaps in 11 patients with a mean age of 61 years (53–69 years). In 8 patients we used simultaneously 2 flaps, what represents a total of 19 flaps raised.

**Results:** We had in three patients minor complications, such as small dehiscense or local infection, treated by conservative methods. In one patient happened partial necrosis of both flaps, and we had to perform a peri-umbilical rectus abominis pedicled flap. Healing has been achieved in all patients, who were discharged from the hospital without necessity of wound care.

An adequate pelvic filling and a good psychological acceptance of the operation, which, in some cases, made possible sexual activity were reached in all patients.

**Conclusion:** This procedure is a safe surgical technique, which aim is not to prolong survival, but it contributes for a better quality of life.

The psychological benefits and, in some cases, the possibility of sexual activity, the good pelvic filling and better healing were goals reached.

953 PUBLICATION

## Our experience with radiochemotherapy in locoregional advanced cervical cancer

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**Purpose:** To improve locoregional controle for some patients with advanced cervical cancer.

**Material and Method:** Between 1991–1995 in Oncological Institute of Bucharest 438 patients underwent radiotherapy (external irradiation delivering on average 50 Gy on the pelvis followed by intracavitary irradiation up to 30 Gy). Radical colpohysterectomy and pelvis lymphadenectomy could be performed at 371 patients, while in 67 cases this was not possible. These latter patients were elected to be treated with 2–4 cycles of chemotherapy.

**Results:** After chemotherapy 30 out of 67 pts. (44.7%) became able to undergo surgery. Postoperative histological exam showed no malignancy at 50% of them.

**Conclusion:** Although locoregional remission was not obtained in all cases, chemotherapy may be an option to improve therapeutic results.