

optimization, (2) a 3D plan using all slices with dosimetrist-guided optimization and (3) a computer-optimized plan with automatic contouring and constrained matrix inversion (CMI) optimization. The resulting dose distributions (DVH) on the same organs at risk were compared in order to verify that the automatic procedure did at least as good as the classical manual method. Results for the irradiated partial volumes of relevant organs are listed in the following table.

The total planning procedure took about 25 minutes of which less than 10 minutes were needed for human interaction.

**Conclusions:** This automatic technique shows acceptable results concerning the partial lung- and heart volume that was irradiated and the procedure reduces the work at the computer planning level at the expense of some more time at the simulator step (third beam).

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### High-dose-rate intracavitary brachytherapy alone in post-hysterectomy for endometrial carcinoma

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**Purpose:** To evaluate local control, toxicity and survival among patients (pts) with endometrial carcinoma stage I and II submitted to post-hysterectomy adjuvant high-dose-rate (HDR) intravaginal brachytherapy (IVBT).

**Methods and Materials:** Between April 1997 to December 2001, 71 pts with endometrial adenocarcinoma stage I and II who underwent total hysterectomy with bilateral salpingo-oophorectomy including negative lymphadenectomy were submitted to IVBT (HDR), as exclusive adjuvant therapy. The median age of pts was 64 (43-85) years. The surgical staging according (1988 FIGO classification), and histologic grade was the following: pT1b/G1-42 pts, pT1b/G2-18 pts, pT1b/G3-1 pts, pT1c/G2-4 pts, pT1c/G3-2 pts; pT2a/G1-3 pts, pT2b/G3-1 pts. Vaginal BT was given in 4 weekly fraction of 6 Gy, prescribed at 5 mm depth from applicator surface. Toxicity was evaluate according to EORTC/RTOG score

**Results:** With a median follow time of 34 (12-68) months, 70 pts are alive and one patient died with breast cancer without evidence of endometrial disease. The 5 years overall survival and disease free survival probability was 98,5% and 93,4% respectively. Recurrence were observed in four pts (5,5%) during the first 2 years: 1 pt experienced a low vaginal recurrence concomitantly with femoral nodes and was submitted to a external beam radiotherapy (EBRT), 2 pts developed a pelvic mass and were submitted to surgery followed by EBRT, and 1 pt with peritoneal carcinomatosis, after 11, 6, 15, and 14 months respectively. The median follow-up time after recurrence was 7,3(3-36) months. All patients were alive at end of the study. The overall late toxicity was low, and no grade 3 or 4 complication were recorded

**Conclusion:** Post-operative intravaginal BT in pts with surgical stage I and II endometrial adenocarcinoma, achieve local control, with minimal morbidity.

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### Definitive radiotherapy for cervical cancers: Retrospective analysis of 449 patients treated with external beam-radiotherapy (EBRT) and high-dose-rate-afterloading (HDR) with more than 5 years follow-up

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**Purpose:** Definitive radiotherapy in the treatment of cervical cancers is a treatment option with excellent clinical results. Presented were the results of a retrospective analysis of cervical cancers how were treated in our department of radiotherapy.

**Material & methods:** Between 1987 -1995; 449 pts. with cervical cancers were treated with a combined treatment schedule with curative intention. The treatment included in all cases external beam radiation (EBRT) and high-dose-rate afterloading with Iridium-192 (HDR-AI). Chemotherapy was not administered. The mean age of all patients was 53 years (27-85 years). The EBRT included in 440 patients only the pelvis, in 9 cases also the paraaortic lymph nodes. The single dose ranged from 1.8-2.0 Gy, the total dose from 38 Gy up to 60 Gy in point B. The HDR-AI ranged in 97% of the cases in 7-8 Gy single dose and 4 to 5 fractions. The total dose in point A was 68-75Gy (in 82% of pts.) and 50-56Gy in point B (96% of pts.).

**Results:** The 5-year-results dependent on tumor stage (FIGO) were: Stage IA and IB (N=87) 87 ± 4%; stage IIA and IIB (N = 155) 79 ± 4%;

stage IIIA and IIIB (N = 194) 53 ± 4%; stage IVA (N = 13) 37 ± 18%. Anemia had also an impact on survival (11g/dL; p

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### Impact of anemia on tumor oxygenation and clinical outcome in cervical cancers treated with definitive radiotherapy

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**Background:** Hypoxia in general is a complex phenomenon. The presence of hypoxia in malignancies is associated with a decrease of prognosis. Anemia in patients with cervical cancers is also an independent predictor in poor outcome. In our investigation we have determined anemia and tumor oxygenation as prognostic factors in advanced cervical cancers who were treated with radiotherapy with regard to correlation of anemia and tumor hypoxia.

**Material and Methods:** 87 patients with locally advanced squamous cell cervical carcinoma FIGO IIB-IVA were investigated from March 1995 to Dec. 2000. All were treated with definitive radiotherapy with curative intent by a combination of external radiotherapy plus HDR-afterloading. The tumor oxygenation was measured using the Eppendorf-device prior to the radiotherapy and after 19,8Gy.

**Results:** The 3-year-survival was in stage IIB 72% (N=19); IIIB (N=59) 60%; IVA (N=9) 22% (total 57%). Our investigation showed a significant impact of change of tumor oxygenation during radiotherapy on survival: Cancers with high median pO<sub>2</sub> prior or during radiotherapy had a 3-year-survival of 68% in comparison to cancers with persisting hypoxia (38%). The survival of anemic patients (hb < 11g/dl) was significantly lower (31%) than of non-anemic patients (64%), p = 0,04. A correlation between hemoglobin-level and tumor-hypoxia during radiotherapy after 11 fractions was observed (p < 0,01). In a multivariate analysis only tumor stage (p = 0,003) and hemoglobin-level during radiotherapy showed a significant impact on overall survival (p = 0,005) and local response (p = 0,0001). The tumor-pO<sub>2</sub> measured after 19,8 Gy had a correlation to local control (p = 0,042). The pO<sub>2</sub>, measured prior to radiotherapy, was without importance on clinical outcome.

**Conclusions:** Advanced stage and hemoglobin level during radiotherapy are independent prognostic factors in cervical carcinomas. In summary, the association between hemoglobin and hypoxia during radiotherapy suggest the importance of hemoglobin substitution in anemic cancer patients during radiotherapy.

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### Hemoglobin levels during radiation therapy and their prognostic influence on local control and survival of patients with endometrial carcinoma

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**Background:** Anemia is a common complication of cancer that has been associated with poor response to treatment and decreased survival in a number of malignancies.

**Material and Methods:** A retrospective chart review was undertaken to determine the effects of hemoglobin levels, measured prior to and during radiation therapy, clinical prognostic factors (e.g. age, body mass index, tumor stage) in altogether 996 endometrial cancer patients treated between 1986 and 1998. Most of them received adjuvant radiotherapy (724/996; 72.7%) but also many underwent primary radiotherapy, in particular because of concomitant diseases, e.g. which did not allow general anesthesia (185/996; 18.6%). None of the patients received recombinant human erythropoietin. Classification of anemia followed WHO recommendations (anemia < 11 g/dL). The difference between observed overall survival and its predicted value was computed by multiple regression analysis for each patient with respect to prognostic factors.

**Results:** Preoperative hemoglobin levels were of no prognostic value. Normal hemoglobin levels prior to treatment showed a trend towards improved survival in patients undergoing primary radiotherapy (p < 0.1). Anemia, however, was significantly associated with poor survival in patients undergoing adjuvant radiotherapy (p < 0.001). The course of hemoglobin during adjuvant radiotherapy played an important role. Survival was improved in patients without anemia compared to patients who developed anemia, who were anemic during radiotherapy, or those whose hemoglobin

levels normalized during treatment (Log Rank = 22.0; df = 3; p = 0.001). Cox regression analysis considering stage, age and body mass index confirmed these findings. Local recurrences were also less frequently observed in patients with normal hemoglobin levels (p = 0.044).

**Conclusions:** Hemoglobin levels at diagnosis may lack prognostic value perhaps due to the incidence of severe vaginal bleeding even in cases with favorable outcome. However, hemoglobin levels prior to and during radiotherapy seem to be important with respect to treatment outcome for endometrial cancer. This finding supports the use of measures to maintain adequate hemoglobin levels (transfusions, erythropoietin) to improve local control and patient survival.

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### Definition of vaginal doses in intrauterine high dose rate brachytherapy

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**Introduction:** The proximal vagina has been traditionally considered resistant to high radiation doses relative to the rectal and bladder mucosa in gynecological HDR and HDR brachytherapy. The aim of this study was to evaluate dosimetric aspects of HDR intrauterine brachytherapy applications and to propose a definition of vaginal points for dose reporting.

**Patients and methods:** HDR brachytherapy was performed using the MicroSelectron system (Nucletron<sup>®</sup>, Holland) using the Fletcher-like tandem and ovoid applicators. Doses were prescribed at points A, and ICRU rectal, bladder and point B doses were recorded for each treatment. Doses to the vaginal mucosa were assessed using 2 sets of points for each ovoid as follows: 5 points on the uppermost surface and 5 points on the lateral surface of each ovoid opposite the five active dwell positions at a distance equal to the radius of the ovoid. Fifty treated patients were chosen for the analysis. Repeatability and reproducibility was analyzed using the ANOVA method. For each patient the total vaginal dose for the whole treatment was calculated. The average dose for both ovoids was determined and the ratio of this dose to point A dose was calculated.

**Results:** Repeatability and reproducibility were found to be less than 1% compared to patient-to-patient variations (> 99%) for all points. The number of fractions, as well as the number of patients in which the middle ovoid point was representative was calculated for the lateral (94%, 98%) and upper (71%, 83%) surfaces respectively. The calculated vaginal-average to point A dose ratio was found to be (lateral and upper surface) 175% and 130% for the 20mm and 25mm ovoids respectively.

**Conclusions:** The proposed method has been validated and allows calculations of vaginal doses according to the given definitions. The use of the middle ovoid point on the lateral surface remains optimal in real applications and is the most suitable for comparisons. Vaginal-to-point A dose ratios were found for the intra-uterine HDR brachytherapy applications and shown to allow a fast estimation of the vaginal dose for 20mm and 25mm ovoids. **Acknowledgement:** The authors acknowledge the support of the NCI/Middle East Consortium, for the fellowship of Dr. Y. Gokcen from the Ege University Medical School, Izmir, Turkey at the Rambam Medical Center, Haifa, Israel

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### Levels of antioxidant proteins in serum of patients with cancer during radiotherapy

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**Background:** The acute phase response also involves changes in plasma concentrations of a number of liver-synthesized proteins. Some of them are C-reactive protein (CRP), ferritin (FER), transferrin (Trf) and ceruloplasmin (Cp).

**Aim:** To investigate serum CRP, FER, Trf, and Cp levels in patients with cancer before, 3<sup>rd</sup> week and completion of radiotherapy (RT).

**Material and Methods:** Determination of serum CRP, FER, Trf, and Cp were performed in 52 patients with inoperable head and neck cancer (n = 11), inoperable esophageal cancer (n = 10), rectal cancer (n=9; operation was performed = 5, inoperable=4), and lung cancer (n = 23) who were treated with radical radiotherapy between February 2001 and March 2002. All patients received 50-64 (median: 60) Gy RT with 2 Gy/fraction using Co<sup>60</sup> treatment machine. Serum CRP, FER, Trf and Cp levels were determined nephelometric method (Beckman Coulter, Image Immunochemistry System,

USA). The statistical comparison of results has been performed by using paired samples Student's t test.

**Results:** Postradiotherapy CRP levels were significantly higher compared to the preradiotherapy levels (p<0.001). We found decreased serum Trf levels while acute-phase proteins such as CRP, FER, and Cp levels increased during RT period (Table). We compared CRP, FER, Trf, and Cp levels in lung cancer patients (n=21) and other patients group (n=31). Statistical analysis did not show any significant difference in CRP levels between two groups. Before, 3<sup>rd</sup> week and postradiotherapy ferritin levels were higher in the lung cancer patients group (p<0.001). Transferrin levels significantly lower in lung cancer patients compared with others before and 3<sup>rd</sup> week of radiotherapy (p<0.01). The statistical analysis yielded a significantly higher levels in only Cp at 3<sup>rd</sup> week of radiotherapy (p<0.01).

Table. Changes acute phase proteins during radiotherapy in all patients

	Beginning of radiotherapy (Mean± SEM)	At 3 <sup>rd</sup> week of radiotherapy (Mean± SEM)	End of radiotherapy (Mean± SEM)
CRP	0.70± 0.12	1.82± 0.66	2.74± 0.61 <sup>c</sup>
FER	213.61± 28.07	299.48± 39.80 <sup>c</sup>	420.55± 50.98 <sup>c</sup>
Transferrin	194.15± 6.24	186.57± 6.24	173.81± 7.33 <sup>c</sup>
Ceruloplasmin	43.88± 1.17	46.71± 1.46 <sup>a</sup>	48.73± 1.33 <sup>b</sup>

a, p<0.05; b, p<0.01; c, p<0.001, compared with beginning of radiotherapy.

**Conclusion:** External beam RT decreased serum Trf levels during irradiation period while other acute-phase proteins such as CRP, FER, and Cp levels increased. Further studies on the roles of the other acute phase reactants and above mentioned parameters in large patients with cancer group during radiotherapy are required to understand the role of markers which alter during radiotherapy.

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### Respiratory gated radiation treatment system using a 3-D ultrasound device

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**Background:** We have developed a new respiratory-gated radiation treatment system using a three-dimensional (3-D) ultrasound device, which allows us to detect the real-time location of the moving tumors in the abdomen. The proposed system is consisted of the 3-D ultrasound device, a 3-D digital localizer, and an image-processing computer.

**Material and methods:** Both CT images and the 3-D ultrasound volume data are acquired at the treatment planning time. The ultrasound data and the position and orientation of the 3-D ultrasound probe are transferred and stored in the image-processing computer, because the 3-D ultrasound probe is tightly attached to the 3-D digital localizer which is fixed on the CT couch. The coordinate system of the CT images is correlated to that of the 3-D ultrasound volume data through the 3-D digital localizer coordinate system. Therefore, the target ROI position delineated on the CT images is transferred to the ultrasound volume data by obtaining the transformation matrix between the CT coordinate system and the ultrasound coordinate system. Real-time ultrasound data of three orthogonal planes are acquired at the treatment time and also transferred to the image-processing computer. Subsequently, the real-time ultrasound image correlation in the target ROI is calculated using the treatment planning phase ultrasound data and the treatment phase ultrasound data, after performing real-time coordinate transformation by employing the 3-D digital localizer. A trigger pulse to the linear accelerator is generated only when the correlation index between the treatment planning phase and the treatment phase ultrasound image data exceeds a predetermined threshold level. We have made a dynamic phantom which has several balls embedded having different radii. The balls are moving within 2 cm according to virtual respiratory cycles.

**Results:** Experiment has been performed on this system with the dynamic phantom to determine its feasibility. The trigger pulses were completely generated only when the tumor position in the treatment is the same position as the treatment planning phase without significant errors.

**Conclusions:** This system can improve the accuracy of the radiation therapy for the moving tumors in the abdomen and allows us to perform stereotactic irradiation for them.