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Title:Primary Radiation Treatment (RT) in 436 patients with carcinoma of the uterine cervix (CU): Analysis of prognostic factors.

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Purpose: To select patients with poor prognostic factors who eventually could be candidates for entering in prospective studies using multimodality treatment . To evaluate complications.

Methods: From 1970 to 1993 , 436 out of 1163 consecutive patients with CU were treated with RT alone. A Cox regression analysis of factors influencing the overall survival (OS) and pelvic control (PC) was performed: a) host/tumor related: age, FIGO stage, pathology, differentiation grade, vascular invasion, presence of hydronephrosis , lymphangiography / CT nodal status, hemoglobin level, comorbidity; b) treatment related factors: energy, radiation technique, doses, boost to lateral pelvis, field edges, central blocking, brachytherapy doses;c) other factors: period, tumor response within 3 months .

Results: Significant detrimental factors for OS: higher FIGO stages, adenocarcinoma pathology, age less than 50 years, presence of hydronephrosis and brachytherapy doses. Detrimental factors for PC were higher FIGO stages, presence of hydronephrosis, low external beam doses and not using a central blocking. For both OS and PC a complete regression within 3 months was a very favourable factor. Sites of failure were: pelvic 17% (74), distant blood borne 6% (25) , distant lymphatic 47% (17), distant combined 3% (12), local plus distant 8% (37%), no failure 62% (271). The G3 complication rate in patients alive was 8% (2% definitive, 6% temporary). The actuarial complication rate in the whole group of was 20% at 5 and 10 years. Age and status were the only factors influencing the complication rate.

Conclusion: The prognosis of patients with CU stages IIB, III and IV, young ages and adenocarcinoma is relatively poor. Prospective studies using multimodality treatment are warranted .

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TITLE: ACCELERATED HYPERFRACTIONATED RADIOTHERAPY FOR LOCALLY ADVANCED CERVIX CANCER.

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Purpose: A phase II trial was designed to evaluate the toxicity and outcome of patients with locally advanced cervix cancer treated with accelerated hyperfractionated radiotherapy (AHFX).

Methods : In this prospective trial AHFX doses of 1.25 Gy were administered twice daily at least 6 hours apart to a total pelvic dose of 57.5 Gy. A booster dose was then administered via either low-dose-rate brachytherapy or external beam therapy to a smaller volume.

Results: Sixty-one eligible patients were enrolled in this protocol; 3.2% had Stage IIB; 68.9% had Stage III; 13.1% had Stage IV and 14.8% had recurrence. Fifty-two patients (85%) completed the planned external beam without a treatment break. Thirty patients had acute toxicity that required regular medication. One patient died of acute toxicity. Fifty-five patients received booster therapy; 45 with intrauterine brachytherapy; 6 with interstitial brachtherapy and 4 with external beam.
The median follow-up of surviving patients is 6 years. Overall 5-year survival is 27% and 5-year relapse free survival is 36%. The actuarial local control rate was 64%. Severe late complications were observed in 7 patients (actuarial rate of 27%). Five patients required hip replacement.

Conclusions: The local control rate was favourable, however, overall survival was not due to the high number of patients who developed metastatic disease. The severe late complication rate was high.

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HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) IMMEDIATELY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCER (LARC).

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Purpose: To analyse locoregional control (LC), disease free survival (DFS) and survival (S) as a function of R0 or R1 resection in LARC (cT3-cT4, any N or cT1-cT2,cN+) after HART.

Patients and Methods: Eighty seven patients with LARC were included prospectively in a trial on preoperative HARTimmediately followed by surgery. All pathological specimens were reviewed for the assessment of margin status with special focus on the radial margin. The survival estimates were computed by the product limit method. Testing for difference in outcome between groups was performed using the log-rank statistics and the general Wilcoxon test.

Results: All 87 patients are treated according to protocol 93-01 (41.6 Gy in 26 fractions, 1.6 Gy b.i.d; immediately followed by surgery - the median time interval between HART and surgery is 5 days). The pathology reveals 77% pT3 and pT4 compared to 99% cT3-cT4, with a 56% incidence of positive nodes essentially pN1 (60%). The R_0 resection rate is 83%. The median follow-up is 2 years. Nine % of patients have liver metastases detected at surgery. The two years S is 81% for patients with R_0 resection versus 48% in case of positive margin ($p<0.05$); the LC is 98% and 66% and the DFS is 69% and 40% respectively.

Conclusions: Positive resection margin after preoperative HART yields a significant survival difference at two years. Distant metastases are the main reason of death in both cohorts (R_0 and R_1): therefore, a phase I study of combined chemotherapy (using a « radiosensitizing » drug) and HART is under preparation.

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Influence of positioning of patients and irradiation technique on the normal tissue complication probability of patients irradiated because of rectal cancer.

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PURPOSE: A prospective study was undertaken to evaluate the influence of both the positioning [prone (PP) vs. Supine (SP)] and the irradiation technique on the normal tissue complication probability (NTCP) of patients postoperatively irradiated because of rectal cancer.

MATERIAL & METHODS: In 20 patients a CT-scan was done in PP (using a belly board) and in SP. The volume of small intestine (SI) and bladder (B) and a standard target volume (TV) of postoperative irradiation of rectal cancer was defined in each axial CT-slice. A 3-, a 4- and a opposing field-technique (FT) with individual absorbers was planned using a 3-D-planning system. The NTCP was calculated by the model of Lymann and Kutscher using the data of Emami. To evaluate the possible late toxicity the α/β was 2.5, for acute toxicity it was 10.

RESULTS: The average volume of SI/B within the TV was 74/35.5ccm for PP and 108.6/63.9ccm for SP ($p<0.002$). Median dose to SI/B was 33/46.4% for PP and 47.8/68.7% for SP ($p<0.001$). The NTCP of SI was 1,6% in PP and 3,7 in SP ($\alpha/\beta=10$, $p<0.001$), respectively 1.1% and 2.7% ($\alpha/\beta=2.5$, $p<0.001$). Median dose to SI/B was 30.8/44,7% for 3-FT, 54.5/60.3% for 4-FT and 94.7/99.6% for opposing FT ($p<0.001$). The NTCP of SI/B was 1.2/0.0% for 3-FT, 0.9/0.0% for 4-FT and 9.0/5.9% for opposing FT ($\alpha/\beta=2.5$), and 1.6/0.5% for 3-field, 1.3/0.0% for 4-field and 11.9/8.7% ($\alpha/\beta=10$) (3-FT/4-FT vs. opposing FT $p<0.001$).

CONCLUSION: Using PP with a belly board and a 3- or 4-field-technique the irradiated volume of and the average dose to SI and B and as a consequence of this the probability of side effects can be reduced significantly