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TREATMENT OF INVASIVE BLADDER CANCER- IS THERE A ROLE FOR NEOADJUVANT CHEMOTHERAPY?

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We re-analysed an early group of bladder cancer patient records in order to extract 2-year survival rates which we could then compare to those now available for more recent patients, treated with modern neoadjuvant chemotherapy.

The earlier, "non-neoadjuvant" group (referred 1975-86) consisted of 348 patients with localized pelvic disease; 315 of these received 40 or more Gy external beam irradiation while 33 got an initial 20 Gy followed by radical cystectomy. The later "neoadjuvant" group (1988-91) contained 56 patients, all of whom received 2 cycles of MCV followed by definitive radiotherapy (40+ Gy) and concomitant cisplatinum in 3 courses. Patients with residual disease after MCV underwent radical cystectomy.

Overall 2-year survival for the non-neoadjuvant group was 62% and for its Stage B1 and B2 subsets, 84% and 60% respectively. The comparable figures for the adjuvant chemotherapy group were overall survival, 60%, and combined Group B survival, 96%. At 2 years, survival for Stage C patients in both groups was 45%. For Stage D1 patients without chemotherapy, 2-year survival was 43%; with neoadjuvant therapy, 23%. 2-year survival for Grade II histologies was 78% without chemotherapy and 82% with it. Grade III patients had 59% survival without chemotherapy and 55% with it.

These very similar outcomes may reflect differential selectivity in assigning patients to either group or indeed, no real effect of chemotherapy. Randomized prospective studies would facilitate an answer.

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NEOADJUVANT TREATMENT FOR LOCALLY ADVANCED BLADDER CANCER: A RANDOMIZED PROSPECTIVE CLINICAL TRIAL

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In December 1988 the GISTV (Italian Bladder Study Group) started a multicentric randomized phase III study to compare neoadjuvant chemotherapy + cystectomy (arm A) versus cystectomy alone (arm B) in locally advanced urothelial bladder tumors (T2-4, N0, M0). The chemotherapy treatment was M-VEC, where Doxorubicine of M-VAC (A. Yagoda) was replaced with its analogue Epidoxorubicine at the dose of 40 mg/m2. Recruitment has been closed in June 1992 with 171 patients enrolled; 134 pts.(arm A 68 pts., arm B 66) have completed the planned treatment and are evaluable. The accuracy of clinical vs pathological staging (arm B pts.) has been 45,5%, with 21,3% overstaged and 32% understaged patients. In arm A the observed objective responses were: CRc 30,9% (CRp 23,5%), PRc 17,6%. Myelotoxicity (WHO 2-3) caused the omissions of d 15 in 20,6% in the first cycle and in 35,8% and 40% at the second and third respectively. D 22 were omitted in 8,8%, 19,9% at the first and second cycle and 23,1% at third. So far the number of odds events are equally distributed in both arms. Preliminary data on DFS and OS do not show any differences between treatment arms.

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A PROGNOSTIC INDEX IN PATIENTS WITH METASTATIC OR RECURRENT TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM (TCU).

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Several prognostic factors for survival have been reported in patients (pts) with disseminated TCU selected for chemotherapy. This study is a retrospective evaluation of 215 consecutive pts admitted with disseminated disease regardless of further treatment. At the time of evaluation, 212 pts were dead from TCU, while 3 pts were lost to follow up. Median survival was 4.3 months. The prognostic significance of 34 clinical, biochemical, and pathological variables were analyzed. Fourteen variables were significant in univariate analyses: Performance status (PS), T-stage, local disease, hydronephrosis, haemoglobin, leukocytes, trombocytes, S-aspartate aminotransferase, S-alkaline phosphatase (SAP), S-lactate dehydrogenase, S-creatinine (CREA), bone metastases, bone marrow metastases and chemotherapy. However, in multivariate analysis the only factors of independent prognostic significance were PS, SAP and CREA. A prognostic index was generated based on combinations of PS and normal or elevated SAP and/or CREA:

Covariates		N	Relative risk	Survival rates
PS	SAP and/or CREA		for death	at 6 months
0-4	Normal	48	1.00	63%
≤2	Elevated	75	2.00	40%
>2	Elevated	38	3.99	16%

The model will be evaluated in a prospective study, and if the results are confirmed, it could be used when comparing outcome of treatment.

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Preliminary results of chemotherapy with Ifosfamid and VP 16 in advanced urothelial carcinoma

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Since 1990 31 patients with advanced urothelial carcinoma were introduced to this phase-1-study to investigate efficiency and toxicity of the following chemotherapeutic regime:
Ifosfamid 1.5 g/m² i.v. day 1–5, and VP 16 120 mg/m² i.v. day 1–5.
Each course was repeated after 21 days. The average investigation period of these 31 patients concerning response and toxicity was 25 months. Median patient age was 66.0 years. 42% presented with a non-resectable advanced tumor (pT3–4, N0, M0). Regional lymph node metastases were detected in 19.0% and distant organ metastases in 39% (M1). In all cases histopathology showed urothelial carcinoma of varying differentiation (G2–G3). 3 to 15 courses of chemotherapy were applied. The rate of response was 51.0%, complete remission was achieved in 35.0%. Within the investigation period three non-responding patients died. Alopecia was noted in each patient, leukopenia (grade I and II) in 12%, polyneuropathy in 8%. There were no deaths induced by chemotherapy. In comparison to MVEC-chemotherapy we found similar response-rates and definitely reduced toxicity.
These preliminary results proove Ifosfamid and VP 16 as a potent combination drug design for chemotherapy of advanced urothelial carcinoma of the urinary bladder with moderate toxicity.
Prospective studies will have to investigate the place value of this therapeutic scheme in comparison to MVEC-polychemotherapy.

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SALVAGE CYSTECTOMY AFTER RADICAL IRRADIATION FOR BLADDER CANCER

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The overall 5-year survival rate in 46 patients who underwent salvage cystectomy after radical irradiation for bladder cancer was 43%. There was a higher 5-year survival in patients with an incomplete response (IR) compared to those with a complete response (CR) to their prior irradiation (50% and 36%), with grade 1 or 2 compared to grade 3 histology (75% and to 28%) and those with T1 or T2 tumours compared to T3 tumours (59% and 32%).

A worsening of tumour grade was found at cystectomy 60% of 10 patients who were Grade 1 or 2 at the time of their irradiation. A worsening of disease stage was found at cystectomy in 53% of 19 patients who were T2 at the time of irradiation. Worsening of tumour grade and stage was consistently higher in those with a prior CR compared to those with a prior IR possibly because of the longer interval to diagnosis.

The expectation of a near equivalent survival compared to patients treated with immediate cystectomy may not be justified.

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EARLY DETECTION OF SUPERFICIAL BLADDER CANCER IN VIVO AND COMBINED TREATMENT USING TRANSURETHRAL SURGERY AND RECOMBINANT ALPHA 2b INTERFERON.

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Twenty eight patients with a superficial bladder cancer in phase (1) were treated between October 1990 and January 1992.during the diagnostic stage -when making the endoscopic study - 50 cm. of tetrameti parrosaniline (TCP) or malachite gren (-CH3-CH3-CH3-CH3 -H-H)were instiled intravesically.The (TPC) is maintained in the bladder for 5 minutes,afterthis time,the vesical cavity is wash_ ed.It is then obsedved that the TPC adheres to the mucosa with structural modifications but not to the healhy epitelium.These coloured areas were firrstly sbmited to biopsy and then to the T.U.R.Apart from transitional cells cancer,the pathologic anatomy findings microacinar carcinoma,adenocarcinoma and dyspla_ sias.The treatment with Alpha 2b Interferon started with 50000000 UI /week intavesical during 3 months andthen 50000000UI/month during 1 year.**RESULTS.**A sgnificant decrease ofthe number of relap ses,there was only a 6 %.**CONCLUSIONS:**It is our belief that the detection of the whole lesions is a priority for the progno_ sis of this multicentric disease.We recommend the TPC for the diagnosis ,Interferon and T.U.R. for the tretment.