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# THE ROLE OF IRIIDIUM 192 & ELECTRON INTRAOPERATIVE RADIOTHERAPY IN THE CONSERVATIVE TREATMENT OF BLADDER CARCINOMA

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**Aim of study:** To analyze the results of 2 pilot studies using Iridium 192 for tumor of the dome and IORT for tumor of the fixed part of the bladder.

**Patient and treatment:** Tumor of the dome: 27 pts treated between 1980-93 for urothelial carcinoma—pT1: 6, pT2: 7, pT3: 14, pN1 4/21 lymphadenectomies. Treatment: preop RX (10, 50 Gy/3F/3D) partial cystectomy ± lymphadenectomy. Plastic tube implant technique loaded one week after surgery with 2 Iridium 192 wires (mean length: 7 cm, mean dose 50 Gy Paris system). Tumor of the fixed part: 20 pts treated between 1990-93 for urothelial carcinoma: T2: 14, T3: 7. Treatment: 2 cycles of neoadjuvant chemotherapy (MVC regime) in 14 pts. External beam radiotherapy (EBRT) 48 Gy (ICRU)/24F/5W with 2 concomitant courses of CDDP. IORT is performed 4 weeks after EBRT. Electron 9 MeV 15 Gy (90% isodose).

**Results:** Tumor of the dome: 5 years overall survival 62%. Local control 23/27. No grade 3 late radiation toxicity; good bladder function in all cases. Tumor of the fixed part: One local relapse (in situ). Four distant metastases. One pubic bone necrosis. Four asymptomatic bladder radiation ulcerations. Good bladder function in all cases. We recommend 12 Gy with IORT.

**Conclusion:** Conservative treatment of bladder cancer is a major challenge. Radiotherapy ± chemotherapy is a promising approach in selected cases. Iridium 192 and IORT are useful techniques for an optimal compromise between local control and toxicity.

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# SELECTIVE BLADDER PRESERVATION BY COMBINED MODALITY THERAPY FOR INVASIVE BLADDER CANCER

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From 1986-1992 106 patients with muscle-invasive bladder cancer treated with induction by combined transurethral resection (TURBT), systemic chemotherapy (2 cycles of methotrexate, cisplatin, vinblastine-MCV) followed by 39.6 Gy irradiation with concomitant cisplatin. Tumor response was then evaluated by cystoscopy, rebiopsy and urine cytology. Complete responders were consolidated with radiation to 64.8 Gy and further cisplatin. Patients with any less than a CR were recommended cystectomy. Median follow-up was 4.4 years. Kaplan-Meier analysis was used to assess outcome.

74 CR patients (70%) and 7 non-cystectomy candidates with <a CR received consolidation chemoradiotherapy. 13 incomplete responders (12%) and 7 patients who could not tolerate induction therapy, underwent immediate cystectomy. 5 died of treatment related toxicity during induction chemotherapy. 5 year actuarial overall survival was 52%. For T2 patients it was 63%, for T3-4 45%. 5 year survival with an intact functioning bladder was 43%. No patient required cystectomy for treatment related bladder morbidity.

Survival is comparable to the published results for radical cystectomy and the majority of the long-term survivors retain fully functional bladders.

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# NEO-ADJUVANT M-VAC CHEMOTHERAPY AND BLADDER PRESERVATION FOR MUSCLE INFILTRATING TRANSITIONAL CELL CARCINOMA (TCC) OF THE BLADDER

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Sixty-five evaluable patients (pts) with locally advanced T2-T4 N0M0 TCC of the bladder were treated with 3 cycles of neo-adjuvant M-VAC chemotherapy. 18 (28%) were T2, 22 (34%) were T3a, 21 (33%) were T3b, 4 (6%) were T4a. Pts were restaged clinically by repeat CT scan and TURB, and were to undergo pathologic staging. Partial cystectomy was to be performed in pts with initial monofocal lesions who responded to therapy. As the study evolved, many pts who responded to M-VAC

underwent restaging TURB only. 6 pts had 20-30% dose reductions of all the drugs due to age (72 to 80). The median f/u is 36 months (range 6 ± 78+ months). 44/65 pts (68%) were managed with conservative therapy (TURB or partial cystectomy). 34/44 (77%) are alive, 28 (64%) with a functional bladder. Pts who had downstaging of their tumors to absence of disease (cT0/pT0) or superficial disease, have 2 and 3-yr survivals of 86% and 83%. For pts with muscle-infiltrating tumors after M-VAC, 2 and 3-yr survivals are 89% and 32%. Response to chemotherapy may be the most important predictor of survival. 28/65 (43%) pts have conserved the bladder. Although bladder conservation is feasible in selected patients, they remain at risk for recurrence.

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# PROGNOSTIC FACTORS IN PATIENTS (PTS) WITH INVASIVE BLADDER CANCER (BC) TREATED WITH A BLADDER SPARING APPROACH

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In a series of pts with muscle invading BC treated with a conservative approach a multivariate regression analysis was carried on to evaluate the association of clinical and pathological factors with clinical response and survival. Seventy pts with T1G3-T4 N0 M0 BC were treated with transurethral resection (TUR) and an alternating chemo-radiotherapy (CT-RT). Characteristics of pts were: median age, 65 yrs (range 40-75 yrs); median ECOG PS, 0 (range 0-1); M/F, 64/6; T1G3, 7 pts; T2, 40 pts; T3, 19 pts; T4, 4 pts; G2, 24 pts; G3, 42 pts. The first 18 pts received 4 cycles of CDDP 20 mg/sqm and FU 200 mg/sqm dd. 1-5 during wks 1, 4, 7, 10 alternated with RT (40 Gy during wks 2, 3, 8, 9). The second group of 52 pts received 3 cycles of the same CT (wks 1, 4, 7) (except the last 20 pts who received MTX 40 mg/sqm dd. 1, 8 instead of FU) alternated with 50 Gy of RT (wks 2, 3, 5, 6). Correlation of clinical and pathological features with response and survival:

		Response (P)	Survival (P)
Tumor stage	T1-T2/T3-T4	0.7	0.7
Grade	G1-G2/G3	0.5	0.9
TUR	complete/incomplete	0.0004	0.009
Preop. hemogl.	≤12/>21	0.5	0.8
Hydronephrosis	yes/no	0.6	0.7

In our group of pts the macroscopic radicality of TUR was the only significant prognostic factor. In fact pts with residual macroscopic disease after TUR had a 3.9 higher RR of death than pts with no residual disease.

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# EFFECT OF INTENSIFICATION OF PLATINUM ANALOGUE COMBINATION CHEMOTHERAPY ON SURVIVAL IN PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA

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The survival of patients with advanced urothelial cancer may be improved by use of combination chemotherapy. The present study reports the treatment efficacy in 105 patients with metastatic or recurrent urothelial carcinoma, who received combination chemotherapy with methotrexate and three dose levels of platinum in 3 consecutive phase II studies from 1981 to 1993. Sixteen patients received cisplatin 50 mg/m<sup>2</sup> every second week, 34 patients were treated with cisplatin 100 mg/m<sup>2</sup> every 3rd week, while 55 patients had cisplatin 100 mg/m<sup>2</sup> combined with carboplatin, 200 mg/m<sup>2</sup> every 3rd week. All patients received methotrexate 250 mg/m<sup>2</sup> with leucovorin rescue at each course of platinum. The overall response rate was 14%, 43%, and 41% in the three studies. The median survival was 5.9, 7.3 and 8.2 months and the survival in responding patients was 11.2, 8.8, and 15.2 months. The survival was significantly prolonged in group 3 compared with group 1 and 2. The importance of treatment regimen was retained even after multivariate analysis with potential confounding factors. These data confirms that intensified chemotherapy increases the chances of obtaining a complete response and a long term survival.