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Role of surgery in patients with liver metastases from nonseminomatous germ cell tumors

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Background: The presence of liver metastases (LM) represents an independent poor prognosticator for patients (pts) with germ cell cancer (GCT).

Material and methods: The charts of 43 male pts with metastatic GCT and who have undergone liver resection between 1990 and 1999 were reviewed.

Results: Thirty-three pts (77%) were initially diagnosed with LM and advanced GCT. Ten pts (23%) had metachronous LM occurring after a median interval of 16 months (range, 6103). Median age was 29 years (range, 18-54). All pts had received platinum based chemotherapy prior to the resection of LM, 81% of the pts as first-line and 19% as second-line treatment. Sixty-five percent of the pts achieved a marker negative partial response (PRm-). PR m+ was observed in 23% and PD in 12% of the pts. Twelve pts (28%) had isolated LM after chemotherapy while 31 pts (72%) had residual extrahepatic tumor masses including the retroperitoneum (48%), lungs (42%), mediastinal lymph nodes (5%) (other sites; 5%). Liver surgery included enucleation or single segment resection in 32 pts (74%) and hemihepatectomy or * 3 segments in 11 pts (26%). Resection of LM yielded necrosis in 67% (n=29), teratoma in 21% (n=9) and vital carcinoma in 12% (n=5). Additional resections have been performed in 31 pts revealing necrosis in 61% (n=19), teratoma in 32% (n=10) and vital carcinoma in 7% (n=2). In 12 of 31 pts (39%) histological results differed between the findings in LM and in resections at other locations. After a median follow up of 37 mos (range, 16-216) the calculated 5-yr survival was 76% (CI95%, 58-93%). Univariate analysis identified mediastinal LN involvement, elevated AFP and refractoriness to chemotherapy as negative prognostic factors.

Conclusion: Surgery of residual hepatic lesions either following induction or second-line chemotherapy is a feasible approach. The high rate of vital carcinoma and teratoma found in liver specimens, different histological results at residual tumor locations and the high survival rate achieved, support a multidisciplinary approach including resection of masses at all locations.

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A phase II study testing intravenous (iv) vinflunine (VFL) as second line therapy in patients with advanced transitional cell cancer (TCC) of the bladder.

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Introduction: VFL (Javlor®) is a novel vinca alkaloid selectively fluorinated by superacidic chemistry at the 20'position of vinorelbine. VFL was selected for clinical development on account of its markedly superior in vivo antitumour efficacy, with respect to other vincas, and of its promising phase I results. The aim of this trial was to determine the efficacy and safety of VFL in pre-treated patients (pts) with advanced TCC of the bladder. Pts must have progressed after one line of platinum-containing chemotherapy, given for metastatic or locally advanced disease. Patients and methods: fifty-seven pts (46 males, 11 females) have been analysed by intention to treat (ITT) and 52 are evaluable for response. Median age was 63 (range 42-81) years and median Karnofsky Performance Status 90%. At study start, VFL 350 mg/m2 was given every 21 days. Due to 1 episode of fatal neutropenic sepsis in 1 of the first 6 pts, VFL dose was reduced to 320 mg/m2 for subsequent pts.

Results: a total of 211 cycles, with a median of 4 cycles per patient (range 1-12), were administered. Further treatment related dose reductions were only required in 19 (9%) cycles and dose delays occurred in 11 (7%) cycles. There were 2 further fatal episodes of neutropenic sepsis at VFL 320 mg/m2. Grade(G) 3-4 neutropenia occurred in 32% and 39% of patients, respectively. Other G 3-4 toxicities were: fatigue (16% pts), constipation (12% pts), myalgia (3.5% pts), vomiting (7% pts). G2 alopecia was experienced only in 17.5% of patients. Efficacy data were: 9 PR (17%; 95% confidence interval 8-30%, and 16% by ITT),confirmed by an independent panel, 27 NC (52%), including 5 (10%) non-confirmed PR and 3 MR (6%),16 PD (31%). Estimated median progression-free and overall survival were 3 months (95% confidence interval 2.4-3.8) and 6.4 months (95% confidence interval 4.6-7.6) respectively, with a median follow-up of 4.6 months (range: 0.3 to 15).

Conclusions: VFL has shown substantial activity at the dose of 320 mg/m2, comparable to the most active agents, in the second line treatment of TCC of the bladder, with manageable toxicity. A phase III trial is ongoing to further evaluate VFL in this setting. Final time-related parameters will be presented at the meeting.

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Long-term colorectal, bladder and sexual dysfunction in patients treated with radical radiotherapy for urinary bladder cancer.

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Background: There are only few studies on functional long-term normal tissue morbidity due to radical radiotherapy (RT) for bladder cancer. The aim of this study is to investigate functional long-term bladder-, intestinal- and sexual dysfunction after RT in patients (pts) treated for bladder cancer T1-T4aNx-N1M0.

Material and Methods: In the period 1/1994-6/2001, 270 pts received RT for bladder cancer at the Department of Oncology, Aarhus University hospital, Aarhus, Denmark. All pts were treated with a CT-based three-field technique and individual blocks with a total dose of 60 Gy to the tumour and bladder and a mean of 46 Gy (range: 0-60 Gy) to the internal and external iliac lymph nodes. Sixty-two (23%) pts were still alive and were candidates to participate in a structured telephone interview based on the LENT/SOMA scoring system.

Results: Fifty-three (85%) pts agreed to participate in the study. Mean follow-up was 34 month (range: 18-80 month). Twenty-nine (55%) pts reported changes in bowel function, 15 (28%) with moderate or severe impact on daily activities. Twelve (23%) pts had loose/liquid stools, 6 (11%) pts had more than 5 motions each day and 7 (13%) pts used anti-diarrhoeal medication on a weekly basis or more often to control stool consistency and frequency. Twenty-eight (53%) pts had fecal urgency, 10 (19%) pts had regular episodes of fecal leakage and 4 (8%) pts were using incontinence pads. Twenty-five (47%) pts reported changes in bladder function, 8 (15%) with moderate or severe impact on daily activities. Eleven (21%) pts had frequent urination with less then 2 hours interval. Thirteen (25%) pts had regular episodes with urinary incontinence and 11 (21%) pts were using incontinence pads. Thirty-two (60%) pts had no sexual activity, however, 24 (75%) of these reported that this was not associated with RT.

Conclusion: The present study shows that RT of urinary bladder cancer is associated with considerable long-term side effects. Persistent major dysfunctions are related with diarrhoea, fecal urgency, frequent urination as well as fecal and urinary incontinence.

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Long term toxicity following definitive radiotherapy of prostate cancer: analysis of EORTC study 22863

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Purpose: Late treatment toxicity is analyzed in the multi-centre EORTC trial 22863 evaluating the value of adjuvant endocrine treatment for patients with locally advanced prostate cancer.

Methods: From 1987 to 1995,415 patients from 26 centers were randomized.377 patients were assessable for long term toxicity. Median age was 70 years. At the time of this analysis, median follow-up is 42(3-136) months. Toxicity was evaluated according to extensive review based on follow-up information and additional details of the severity and evolution of the adverse events obtained by comprehensive queries. Urinary and intestinal late toxicity and leg edema were graded according to modified RTOG scale on the basis their severity and impact on patients' performance status. Significant late treatment toxicity was classified as moderate (grade2) when symptoms required brief hospitalization or minor surgical procedures; severe (grade3) when they required a major surgical procedure or prolonged hospitalization;and fatal (grade4). Late SAE, that included cases with late treatment toxicity, were also assessed and grouped according to their relation to the treatment as; 'likely-related', 'not assessable' and 'unrelated' to treatment.

Results: 291 patients(77%) had either no or mild (grade1) late toxicity. Of the 86 patients with ≥grade 2 late toxicity;72 had grade 2, 10 grade 3 and 4 grade 4.The most frequent major urinary and intestinal complications were urethral stricture and proctitis, respectively. All 14 events of ≥ grade 3 toxicity except 2 (intestinal toxicity; small bowel obstructions) were due to urinary complications. The most frequent ≥grade 3 urinary toxicity was urethral stricture (9),followed by urinary incontinence (2) and cystitis (2). Late SAE were reported in 34 patients (9%) as likely-related(15 cases; 14 with≥grade 3 late toxicity and 1 with severe proctitis requiring blood transfusion), unrelated (7)and not assessable (12).

Conclusion: In our series,the overall toxicity is comparable to those reported in the literature, except for 4 patients, died due to urinary complications. Our analysis includes comprehensive queries which might have led to a more complete data collection than other series. It seems relevant to address carefully the occurrence of adverse events that are not clearly related to treatment, since the symptoms attributed to concomitant pathologies are, at least partially, due to the treatment side-effects.

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HDR vs. IDR brachytherapy for bladder cancer: disappointing local control and unexpected late toxicity

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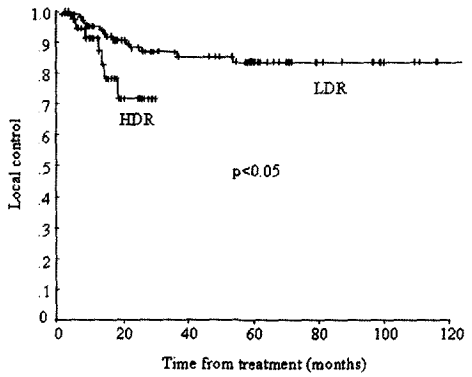
Objective: To analyze of the efficacy and toxicity of a high dose rate (HDR) brachytherapy schedule of 10 x 3.2 Gy for T1G3 and T2 bladder carcinoma and to compare these results with a previously used schedule of 40 Gy low dose rate (LDR) brachytherapy.

Patients and methods: Between 2000 and 2002 40 patients with T1G3 and T2 bladder carcinoma have been treated with 30 Gy external beam radiotherapy (EBRT) followed by interstitial HDR brachytherapy 32 Gy, 10 x 3.2 Gy/2 fractions per day with 6 hr interval. Local control rate and toxicity is compared with a historical group of 108 patients treated with 30 Gy EBRT followed by 40 Gy interstitial LDR brachytherapy. The HDR schedule was designed to be biologically equivalent to the previously used LDR schedule with the linear quadratic model including incomplete mono-exponential repair. The following parameters were used: for late responding normal tissue a/b ratio = 3 Gy and half time of repair = 1.5 hr; for tumor a/b ratio = 10 Gy and half time of repair =0.5 hr.

Results: After a median follow up of 14 months 7/40 HDR patients developed a local recurrence, at 20 months of follow up local control was 72% for HDR vs. 91% for LDR LDR ($p<0.05$). The incidence and pattern of late toxicity EORTC/RTOG > G3 was different for the two treatment groups. In the HDR group 5/30 evaluable patients encountered serious late toxicity, 4 patients developed global bladder dysfunction and one patient developed a local ulcer at the site of implant. In the LDR group 2/84 evaluable patients developed serious late toxicity, one patient developed a persisting vesico-cutaneous fistula and the other a urethral stricture due to fibrosis, both because of local problems at the site of implant. The difference in observed late toxicity HDR vs. LDR was highly significant (p=0.006).



Conclusions: Local control of HDR brachytherapy for bladder cancer was disappointing and late toxicity unexpectedly high when compared with the originally used LDR schedule. The results can be explained by the selection of the values for a/b ratio and repair half time when calculating equivalent schedules. The lack of reliable data on human tissue repair kinetics and repair capacity, the heterogeneity of LDR dose rates and essential differences in biological dose distribution make the calculation of equivalent HDR schedules hazardous.

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Does the clinical outcome correlate to altered expression of the EGF Receptor-family in renal cell carcinoma?

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Background: The EGFR family is involved in the development of many tumors. EGFR (ErbB1, HER1) is believed to be involved in the tumorogenesis of renal cell carcinoma (RCC). ErbB2 (HER2, neu), ErbB3 (HER3) and ErbB4 (HER4) has been poorly or not at all investigated in RCC. EGFR and ErbB2 are known to act as oncogenes in many tumors. Data on ErbB4 suggest that it acts as an oncogene in some tumors (colon cancer, medulloblastoma) but counteracts tumor progression in some (breast cancer).

Aim: To evaluate the expression of the EGFR family members in RCC, and correlate the levels to various clinical parameters.

Material and methods: Tissue samples from 100 patients with RCC and samples of non-neoplastic kidney cortex from the affected kidney were analyzed by real-time RT-PCR. Immunohistochemistry with antibodies against the EGFR and ErbB4 was performed on tumor tissues and kidney cortex in 8 cases.

Results: Results from the 20 cases with tumor and matched non-neoplastic kidney tissue showed that EGFR is up-regulated, ErbB2 and ErbB4 is down-regulated in the tumors. ErbB3 expression was not significantly altered. The immunohistochemical results correlated with the RT-PCR results.

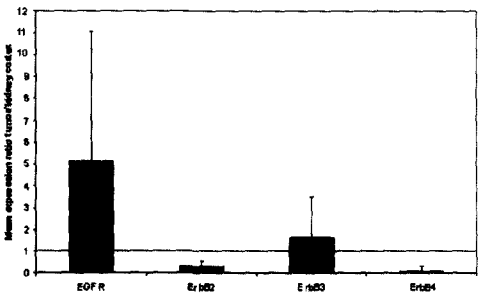

Figure: Ratio of EGFR-family members expression between tumor and matched non-neoplastic kidney cortex. Mean and stadard deviation from 20 cases.

Conclusions: The results confirmed the up-regulation of EGFR in RCC. ErbB2 was down-regulated in RCC. The marked down-regulation of ErbB4 suggests that it may be an important tumor suppressor in RCC. More investigation is needed to elucidate the role of these proteins in RCC. Data on analysis of 100 tumors with correlation to clinical parameters will be presented.