

DEDICATED TEACHING PROGRAMS CAN IMPROVE THE QUALITY OF TUR OF NON-MUSCLE-INVASIVE BLADDER TUMOURS (NMIBT): EXPERIENCE OF A SINGLE INSTITUTION

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Introduction & Objectives: The quality of surgery (TUR) may affect the 3 month recurrence rate (3-RR) in pts with NMIBT, the correct stage and the final outcome of the disease. A great variation in the 3-RR between European centre was reported by EORTC and this was not due to clinical factors but to the surgeon. Recent reports showed a low rate of muscle in path specimen after TUR (39-60%) causing possible staging errors. Endoscopic teaching has a major impact on surgical formation of young urologists and can result in a better prognosis for patients with NMIBT. The aim of this study was to evaluate the modification in time (2000-2005) of the 3-RR between surgeons of the same centre, the rate of muscle in the specimen and the complication rate after a dedicated teaching program has been started in 2002.

Material & Methods: From 2000 to 2005 1048 TURs of NMIBT were performed: 181 in 2000, 177 in 2001, 171 in 2002, 142 in 2003, 205 in 2004, 172 in 2005. Data on the 3 parameters (3-RR, Muscle in the specimen and complications) starting from 2000-2001 were taken as baseline. In June 2002 we started a dedicated teaching program on surgical treatment of NMIBT. The program included the following: for Diagnosis: a) routine use of flexible cystoscopy and bladder diagram to identify and better localize tumours in the bladder. For surgery: a) video-TUR as the standard treatment with imaging archive b) bipolar resectoscope use (after 2005) c) a senior urologist in the OR as tutor, controlling the procedure. Teaching session meetings on bladder tumours held every 15-30 days, together with daily case presentation and discussion were also included in the program. Pathological reports of all the resected bladder tumours were always controlled by the most experienced urologists (2), compared to the procedures and discussed with the surgeon who performed the TUR. Future therapeutic decisions were taken accordingly. Also this was part of the program.

Results: In 2000-2001 the 3-RR was 8% for staff members and 28% for residents. The presence of muscle in the TUR specimen was 50% and 56% respectively. Complications: perforation rate=3% Major bleeding=4%. After the dedicated teaching program the 3-RR decreased to 3% for staff members and to 16% for residents. The muscle present in the TUR specimen was 57% in 2002, 69% in 2003, 88% in 2004 and 79% in 2005. Complications: perforation=0.5% Major bleeding=2%.

Conclusions: A meticulous and dedicated teaching program for the surgical treatment of NMIBT can determine a significant reduction in the 3-RR (from 8-28% to 3-16%), in an increase rate of muscle present in the TUR specimen (from 50 to 80%) and a reduction of complications. We encourage the European leading Institutions to adopt these programs in order to improve their results.

CARCINOMA IN SITU OF THE BLADDER: LONG-TERM RESULTS OF A RANDOMISED PROSPECTIVE STUDY COMPARING INTRAVESICAL ELECTROMOTIVE MITOMYCIN-C, PASSIVE DIFFUSION MITOMYCIN-C AND BACILLUS CALMETTE-GUERIN

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Introduction & Objectives: We report the long-term follow-up analysis of a randomized prospective study assessing the efficacy of intravesical passive diffusion mitomycin-C (PD/MMC), electromotive/mitomycin-C (EMDA/MMC) and bacillus Calmette-Guerin (BCG) in patients with carcinoma in situ (Tis) of the bladder.

Material & Methods: Between 1994 and 2001, 108 patients with histologically proven multi-focal Tis of the bladder were randomly assigned to a) 40 mg EMDA/MMC instillation with 20 mA electric current for 30 minutes (n=36); b) 40 mg PD/MMC with a dwell time of 60 minutes (n=36); or c) 81 mg BCG with a dwell time of 120 minutes (n=36). All patients were scheduled for 6 weekly treatments. Non-responders received another 6 weekly treatments while responders received 10 monthly follow-up treatments. The primary endpoints were the complete response rates at 3 and 6 months; secondary endpoints were the disease-free interval, time to progression, overall and disease-specific survival. Analyses were done by intention to treat.

Results: The complete response rates at 3 months for the PD/MMC, EMDA/MMC and BCG groups were 28%, 53% and 56%, respectively (p=0.0361). At 6 months the corresponding rates rose to 31%, 58% and 64% (p=0.0123). After a median follow-up of 82.5 months (range 17.8-148.8) 32/108 patients (29.6%) were disease-free. They included 7 (19.4%) in the PD/MMC group, 12 (33.3%) in the EMDA/MMC group and 13 (36.1%) in the BCG group (p<0.0001). Median time to first recurrence was 9.1 months (95% CI, 6.3-11.8) in the PD/MMC group, 15.0 months (95% CI, 12.2-30.1) in the EMDA/MMC group and 17.8 months (95% CI, 12.2-27.3) in the BCG group (p<0.0001). Progression to muscle invasive disease was reported in 37/108 patients (34.2%), who included 16 (44.4%) in the PD/MMC group, 11 (30.6%) in the EMDA/MMC group and 10 (27.8%) in the BCG group (p=0.0612). Median time to progression was 21.5 months (95% CI, 9.3-24.6) in the PD/MMC group, 26.9 months (95% CI, 20.8-63.8) in the EMDA/MMC group and 27.8 months (95% CI, 5.9-52.9) in the BCG group (p=0.0612). The overall mortality rate was 50.9% (55/108 cases). Death occurred in 19 patients (52.7%) in the PD/MMC group, 17 (47.2%) in the EMDA/MMC group and 19 (52.7%) in the BCG group (p=0.4964). 27 deaths (25%) were due to bladder cancer with 11 patients (30.5%) dying in the PD/MMC group, 8 (22.2%) in the EMDA/MMC group and 8 (22.2%) in the BCG group (p=0.4941).

Conclusions: In patients with Tis of the bladder intravesical EMDA/MMC provides a better response rate and disease-free interval than PD/MMC. As the response rates match those induced by BCG, EMDA/MMC may be an alternative or complementary therapy. However, after all approaches the 3 and 6 month complete response rates and times to recurrence are unreliable predictors of outcome in these high risk patients.

CASE-CONTROL STUDY OF INDEPENDENT METACHRONOUS MALIGNANCIES IN NON-MUSCLE INVASIVE BLADDER CANCER PATIENTS

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Introduction & Objectives: The incidence of urogenital tumours constantly increases due to overproportional aging of the population in industrial nations. Bladder cancer (BCA) has an incidence of 18 cases per 100.000 residents (Ratio Male/Female = 3:1). The follow up for superficial BCA relied so far primarily on the detection of either a relapse or a progression. The aim of our study was to determine the incidence of independent non-urothelial primary tumours in patients with a non-muscle invasive BCA.

Material & Methods: We retrospectively analyzed the charts of 409 consecutive patients (312 males vs. 97 females; overall 710 cases) diagnosed with a non-muscle invasive BCA over a ten years period at our institution. All independent metachronous malignancies were registered and compared to the gender-, age-, and time-specific incidence rates of the Swiss cancer registry.

Results: Mean age at superficial BCA diagnosis was 73.3 years. In 262 (64%) of these patients a stage pTa was detected, whereas in 112 (27%) pT1 was histologically diagnosed. Moreover, 35 patients (9%) histologically showed a carcinoma in situ (pTis). During follow-up, an independent non-urothelial primary cancer manifested in 62 men (19.9%), and 16 women (16.5%). Histological stage of their primary BCA was pTa in 56.6%, pT1 in 34.2%, and pTis in 9.2%. In male patients, prostate cancer was predominant with 26 cases (RR=4.4, p<0.0001). Compared to the age-specific incidence in the general male population, the incidences of bronchial and colon cancers were also high (12 and 5 cases, respectively; RR=4.5 and 2.0, p<0.0001). In female patients, cervical/uterine, breast, and bronchial cancers were predominant with 3 cases each, corresponding to a significantly elevated risk.

Conclusions: Follow-up in patients with superficial BCA should pay special attention to independent non-urothelial tumours. Besides prostate cancer, tumours outside the range of the urological expertise have to be regarded and should possibly be incorporated in the recommendations for follow-up examinations.

P27 BLADDER DYSFUNCTION: WHAT IS NEW ABOUT RECEPTORS AND DRUGS Thursday, 27 March, 12.15-13.45, Blue Hall 1

EXPRESSION AND POTENTIAL CLINICAL RELEVANCE OF AQUAPORINS IN HUMAN UROTHELIUM

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Introduction & Objectives: It has long been accepted that the urinary tract serves as an impermeable transit and storage unit, with the kidney being solely responsible for the composition, final concentration and volume of urine. Preliminary work using a bioinformatics and micro array approach indicated expression of aquaporin (AQP) 3 and 7 transcripts by human urothelium. This finding has not been previously reported. AQPs play a crucial role in water transport mechanisms across biological membranes and are ubiquitous in all kingdoms of life, with 13 different isoforms being identified thus far in the human body. The aim of this work was to obtain molecular evidence that normal human urothelium (NHU) expresses AQPs and to consider potential implications for (patho)physiology of the lower urinary tract.

Material & Methods: To investigate AQP transcript expression in NHU, RT-PCR was used. The expression screen was carried out on multiple independent samples of freshly-isolated urothelium from surgical bladder and ureteric specimens and on proliferating and differentiated NHU cells in culture. Immunolabelling and immunoblotting techniques were employed to study AQP expression and localisation within native urothelium and cultured urothelial cells, respectively. Tissue engineered urothelial constructs have been established and investigated for AQP expression in preparation for future physiological studies.

Results: Transcript for AQP 3, 4, 7, 9, and 11 were expressed consistently by freshly-isolated urothelium as well as in cultures of NHU cells. AQP 0, 1, 2, 5, 6, 8, 10 and 12 were not expressed. Immunocytochemistry confirmed expression of AQP 3 at the protein level. AQP 3 was shown to be localised to the basolateral borders in both urothelium in situ and differentiated tissue constructs in vitro. In proliferating NHU cells, AQP 3 was predominately cytoplasmic but became localised to intercellular membranes upon differentiation.

Conclusions: This is the first study to provide evidence that aquaporins are expressed by human urothelium suggesting a role in water and solute transport across the urothelium. These findings challenge the traditional concept of the urinary tract as an impermeable transit and storage unit and support our hypothesis that the lower urinary tract is able to modify the composition and volume of urine. The predominant expression of AQP 3 is interesting, as it is an aquaglyceroporin which mediates not only water, but also small solute transport such as urea. This could suggest a potential role in transurothelial urea re-absorption and in the regulation of osmolality and cell volume of urothelial cells. Further investigations are required to obtain physiological evidence that urothelium is capable of water and solute transport and to explore the biological relevance of aquaporins within the lower urinary tract.