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## Prevention of Bladder Tumor Recurrence

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The Way to Prevent Tumor Implantation is by Washing out the Cancer Cells and Prevent Its Adherence Prevention of Tumor Recurrence After Transurethral Resection by Means of Bladder Irrigation with Distilled Water - A Prospective Randomized Study with a Long-Term Follow-up.

### 1. Introduction

Superficial papillary tumors of the bladder recur in about 70% of patients in the first 2 years following treatment by transurethral resection (TUR). Since there is no other evidence of mucosal changes in random biopsies it seems that the high recurrence rate is due to tumor implantation. We tried to find out whether irrigation with distilled water of the bladder following TUR will reduce tumor recurrence.

### 2. Material and methods

Sixty nine patients were enlisted for a prospective randomized controlled study in order to investigate the efficacy of bladder irrigation with distilled water for 24 hours following a transurethral resection of first time papillary transitional cell tumors of the urinary bladder. These patients were compared to a group of patients that were not irrigated at all. There were 31 patients in the first group and 38 in the control. All patients had grade 2 transitional cell tumors (average 1.2 tumors per patient). Random biopsies that were taken at the time of operation showed no additional pathology.

### 3. Results

In the irrigated group there were 8 (25%) recurrences in the first 24 months of follow-up while at the same period of time there were 22 (58%) recurrences in the control group,  $p=0.007$  (using a chi square analysis). On longer follow-up of between 2 to 10 years (mean 6 years) there was no difference in tumor appearance between the two groups 8 out of 23 (37%) in the irrigated group and 5 out of 16 (31%) in the remaining patients in the control group,  $p=0.6119$  using the same statistical tool. The recurrence rate of low-grade superficial papillary tumor of the bladder is about 70% (1). Most of the recurrences occur in the first year after the transurethral tumor resection (TUR) and 95% of the recurrence occur within two years after the resection (2). Although this is a low grade malignant tumor and biopsies

that are taken randomly at the time of the resection are normal, the tumor shows a high tendency to recur, and this observation needs some sort of biological explanation. The tumors tend to occur at the bladder neck where the resectoscope most frequently injures the normal mucosa and at the dome of the bladder where distention of the bladder while inflating it during the operation tends to crack the epithelial lining. During transurethral-resection of a bladder tumor many viable malignant cells are floating free in the bladder and have the capability of adhering to a raw surface in the bladder (3). These two facts lead to the idea that the recurrence is iatrogenic: meaning that cells that were floating in the bladder during the TUR are implanted into the injured bladder mucosa. If this hypothesis is correct then elimination of the viable cells and disabling of the adhesive properties of the cells should significantly lower the recurrence rate of this tumor. Distilled water irrigation of the bladder should reach these goals. In order to prove this hypothesis a controlled randomized study was conducted from 1983 until 1990 in which the efficacy of washing the bladder with 12 liters of water in 24h was compared to no irrigation during the post operative period. Tumor occurrences were compared in these two groups at the end of the first two years and from then on.

#### 4. Patients selection

Eighty four patients entered the study, 15 had high grade tumors or carcinoma in situ and the were treated right away with Bacille Calmette Guerin (BCG), therefore the effect of irrigation could not be monitored in them. The remaining sixty-nine patients with first time low-grade superficial transitional cell tumors were studied for the effect of irrigation on tumor recurrence. There were fifty-three males and sixteen females. They were between the ages of 40-90 years old with a mean age of 62. They did not have any other known malignancy and were not treated for any previous diseases in the bladder. The diagnosis of the tumor was made at the outpatient clinic and all patients underwent a standard TUR with random bladder biopsies in order to exclude carcinoma in situ. In all cases previous to the operation urine cytology was sent and IVP was performed and was normal in all studied patients. Randomization was done after the completion of the surgical intervention by blindly selecting a note from an envelope which stated whether or not the patient should be irrigated. In the group randomized for irrigation, the irrigation was through a regular a 20F Folly catheter. In the group randomized for irrigation, instructions were given to irrigate the bladder at a rate two liters of distilled water every 4h for 24h.

#### 5. Results

There were 69 patients in this study. Thirty-one were irrigated and 38 were not. The recurrence rate of the irrigated group within 24 months after the TUR was 8 patients 25%. while the recurrence rate of the non-irrigated patients during the same period of time was 22 patients 58%. The statistical difference between these two groups is  $p = 0.0079$  using a Chi square test. (The recurrence rate of the irrigated patients between 2-10 years with a mean follow-up of 6 years was 7 patients out of the 23 remaining patients 34%. While the recurrence rate of the non-irrigated patients at the same period of time with the same mean follow-up was 5 out of the 16 remaining patients 32%. There was no statistical significance difference between these two groups at this period of time.  $P=0.6119$  using the same statistical analysis. The number of the primary tumors (1.2) was the same in both groups; so were the size of the tumors (1.7cm)

and the mean age of the treated patients appearance of tumor which most probably occurs due to the continued insult by carcinogens to the bladder mucosa.

## 6. Conclusions

Water irrigation of the bladder following a TUR is very effective in preventing early recurrence of low grade papillary transitional cell tumors. It achieves this goal by mechanical expulsion of floating tumor cells and by preventing the cells from adhere.

### Detection of tumors by Raman spectrum

There is a need to detect bladder cancer as early as possible in order to improve cure rate. In order to detect bladder cancer as early as possible to allow effective BCG treatment/ We conducted an experiment using a green laser to find the Raman signal of bladder cancer cells voided in the urine/ The use of Raman Spectroscopy in the diagnosis of bladder cancer from cells voided in the urine Urine cytology is expensive and inaccurate in detecting bladder tumors. The late diagnosis of invasive bladder cancer is a major medical and economical problem because bladder cancer is the fifth most frequent cancer in the western world. Today 85% of patients with high grade tumors, have invasive cancer at diagnosis. To address this problem we use Raman Molecular Imaging (RMI) to improve the accuracy of urine cytology. RMI is an innovative technology that combines the molecular chemical analysis capacity of Raman Spectroscopy with high definition digital image microscopic visualization. Digital imaging information and Raman Spectra show unique "Finger Print" Spectra of the different cells voided in the urine. The goal of this project is show that this method is accurate in the diagnosis of bladder cancer. Methods: Bladder cancer tissue with known diagnosis (10 T<sub>a</sub>.G<sub>1</sub>) (10 T<sub>2-3</sub>. G<sub>3</sub>) and 2 normal bladders were scanned using a FALCON Raman imaging microscope. The typical Spectral Finger print of cells from samples of each pathology was characterized. Tissue samples were compared to voided cells in the urine and the same spectra were obtained from the same pathology. Further measurements on 45, 49 and 50 urine samples from G<sub>3</sub>, G<sub>1</sub> and G<sub>0</sub> cases. Results: Using tissue, the G<sub>3</sub> tumors gave a very high pick of scatter at 1584 cm<sup>-1</sup> Raman shift. G<sub>1</sub> tumors showed a less prominent but a significant elevation at this shift. While G<sub>0</sub> did not show this elevation. Raman imaging showed that the material responsible for the signal was confined to the cells.

Forty nine patients with no tumor showed 0% false positive results. In 45 patients with G<sub>3</sub> tumors 44 (98%) showed the signal of a tumor and 41 (94%) showed that the tumor is of high grade. In 50 G<sub>1</sub> tumors all were detected as tumor and there were only 2 samples that gave the high grade signal. In the RMI there is a distinctive difference between high grade and low grade tumors and non malignant cells. Conclusions: With this more reliable test it will be easier to find this tumor at its initial state. RMI shows that the signal from bladder cancer tissue and cells voided in the urine can be identified and distinguished from normal bladder tissue and cells in a very high accuracy rate and should be used in screening the high risk population.

This study was published in the January 2011 in European Urology. This examination can be performed with the aid of a computer and does not require a pathologist or a Urologist. This presentation details the use of a software algorithm and Raman Spectroscopy to rapidly identify malignancy from cells in voided urine. The spectrum is analyzed by a software algorithm which removes interpreter bias from the analysis.

## 7. Methods

Cellular analysis was performed on urine collected from patients with and without TCC of the bladder. The urine was spun. The supernatant was discarded and the pellet was suspended with distilled water. The process was repeated. The remaining material was placed into a Cytospin chamber which resulted in cells being deposited on an aluminum slide. Each slide was analyzed with the Falcon Microscope. The epithelial cells were photographed using 50x objective magnification. Raman spectra were obtained using 100 objective so as to minimize the empty space around the cell. At first spectra were obtained from 172 slides with an average of 5 cells per slide. The results led to formulation of the algorithm. Then the algorithm was tested on 196 additional cases. Results. The initial 172 samples were as follows: G0-50, G1-50, G3-50, CIS-22. Accuracy was as follows: G0-90%, G1-88%, G3-100%, CIS-95.5%. This analysis served to produce a software algorithm to identify characteristic signals produced by RMI. The algorithm was applied to another 196 samples made up of G0-76, G1-52, and G3-68 were analyzed. The algorithm's accuracy was: G0-90%, G1 57%, G3-97%. Conclusions. RMI of cells in voided urine can accurately distinguish benign from malignant pathology. Application of a software algorithm to the cellular spectrum rapidly and independent of operator bias segregates benign from malignant cells.

### Comparison of BCG types

Since BCG is the most effective treatment in preventing tumor recurrence we conducted a study to find out whether live bacteria or freeze dried one is more effective Comparison of the efficacy and side effects of Pasteur vs. Connaught Bacille Calmette Guerin (BCG) treatment of Superficial bladder tumors One of the unclear area in treating superficial bladder tumors with Bacille Calmette Gguerin (BCG) is which preparation is the most effective one, and what are the relations between successful treatment and the side effects of it.

## 8. Material and methods

In order to find out which preparation of BCG 1) a freeze dried or 2) a fresh living suspension, are most effective and has a lower side effect Material and Methods: A controlled randomized study was done comparing the Connaught Imucyt to the original Pasteur strain. There were 66 patients in the study, 34 were in Pasteur strain and 32 in the Connaught strain. Each treatment consisted of 6 weekly installations of either 175 mg of Pasteur BCG or 108 mg of Imucyt. There were 50 males and 16 females. The mean age was 64 (39-86). Forty five patients had a papillary tumors, 22 grade 2, 20 grade 3, and 3 grade 4. Four patients had a stage A tumor and the rest had stage O tumors. Twenty two patients had Carcinoma In Situ. Results: In a mean follow-up period of 61.5 months the recurrence rate of The Connaught strain was 11 (34%) and in the Pasteur strain 10 (29%) there is no statistical difference between the preparations. The same amount of side effects occurred in both treatments. Not even one patient had to withdraw from the treatment.

## 9. Conclusions

Both Connaught and Pasteur BCG preparations are equally effective with the same amount of side effects. Sixty six patients with recurrent papillary transitional tumor or patients with

biopsy proven carcinoma in situ (CIS) of the bladder were randomly treated with BCG following a TUR or biopsies for CIS. Thirty four were treated by a six weekly Pasteur fresh BCG (150 mg./ treatment) and 32 were treated with Connaught frozen-dried BCG (108 mg./treatment). Their mean age was 64 (39-86), 50 were men and 16 women. The tumor grades were: 22 grade 2, 20 grade 3, and 3 grade 4. Four patients had Ta tumors the rest had T1 tumors according to the ICCU calcification of bladder cancer. Twenty two patients had CIS. The age, grade, stage, sex were equally divided between the two groups. The mean follow-up time was 61.5 months (55-67) In order to find out which preparation of BCG 1) a freeze dried or 2) a fresh living suspension, are most effective and has a lower side effect.

## 10. Material and methods

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In a mean follow-up period of 61.5 months the recurrence rate of The Connaught strain was 11 (34%) and in the Pasteur strain 10 (29%) there is no statistical difference between the preparations. The same amount of side effects occurred in both treatments. Not even one patient had to withdraw from the treatment.

## 12. Conclusions

Both Connaught and Pasteur BCG preparations are equally effective with the same amount of side effects.

## 13. Conclusions

It seems from our study that there is not any difference between the two preparations of Pasteur and Connaught BCG, not in the response to treatment, and not in the side effects. Therefore it is recommended to use any one of these preparations according to the convenience of the treating physician.

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### Treatment of T1 Tumors

In high grade superficial tumors the recurrence of non BCG treated patients is about 90% in 2 years. With BCG treatment our results are: 40 patients with T1 intermediate (G2) and high

grade (G3) bladder cancer were treated in Hadassah university hospital from 1983 to 2001. All the patients were treated by transe-urethral removal (TUR) of the tumor and additional Bacille Calmette Guerin (BCG) immunotherapy to the affected bladder. The mean follow-up to failure, death or to last examination was 120 months (12-228) . There were 32 patients that had no evidence of disease in this period of time. One patient was lost for follow-up 6 months after the diagnosis of his disease. 5 patients had invasive tumor recurrence and needed cystectomy 2 had recurrent low grade superficial tumors and were treated by a TUR. Four patients had metastatic disease on recurrence they all died within 2 years after the methastasis was discovered. They were treated by MVAC chemotherapy (3) or no treatment at all (1).

### **mRNA of IL2 and response to BCG treatment**

We showed in the June 1996 issue of JCO that IL-2 is needed for the activity of BCG Novel Approach to Treatment of Bladder Cancer by Analysis of Interleukin-2 Gene Activation Carcinoma in situ is treated solely with BCG. However, 1/3 of these patients will fail treatment and suffer relapse. In lymphoid cells isolated from bladder cancer patients during BCG treatment, we studied the expression of two genes essential for regulation of an adequate immune response, encoding interleukin-2 (IL-2) and interferon-gamma. IL-2 and IFN-gamma are Th1 cytokines with many critical functions; they are essential for protective immunity and major players in the anti-tumor response. To this end, we developed a method that accurately measures the induced expression of IL-2 and IFN-gamma mRNA in peripheral blood mononuclear cells (PBMC) from only 10 ml of peripheral blood. Our finding is that the ability of the IL-2 gene to be activated is a highly accurate predictive parameter of cure from bladder cancer: 97% of patients whose IL-2 gene is inducible will enter remission. By contrast, up to 90% of patients whose IL-2 gene failed to respond to a stimulus had relapse or persistence of the tumor (Kaempfer et al., J Clin Oncol 14:1778-1786, 1996). Our findings strongly suggest that expression of the patient's own IL-2 gene is essential for mounting an anti-tumor response. This is the first instance of successful prediction of clinical outcome during cancer treatment, well before any symptoms of relapse. Determination of induction of IL-2 mRNA in a patient's PBMC provides feedback on the response of the patient even before termination of treatment. Patients showing a lack of inducibility of IL-2 mRNA thus can receive alternative treatment well before tumors recur. We propose to apply insight gained from analysis of IL-2 gene activation towards rescuing the 1/3 of bladder cancer patients that will fail standard treatment with BCG. Our strategy will be first to identify such patients by the inability of their IL-2 gene to respond to induction during treatment with BCG, and then to subject this subset to a second course of BCG treatment, either alone or in combination with human rIL-2. This combination of BCG and IL-2 was proven safe in a recent phase I study we performed and in a phase II study was more effective than conventional BCG treatment. Such an approach, we postulate, may elicit in these patients the needed anti-tumor response - at an early stage and well before relapse occurs - and lead to cure. We believe that our previous research creates an unusually strong basis for this project, which involves a close collaboration between a molecular biologist (RK) and a uro-oncologist (AS) at Hadassah Medical Center. From a scientific point of view, it will allow rigorous testing of the role of endogenous IL-2 gene activation in the anti-tumor response.

### External IL2 and BCG treatment

As a result of this study we tested the possibility of adding external IL-2 to the BCG treatment Phases I and II in the IL-2 BCG intravesical treatment of bladder tumors. The standard treatment of superficial recurrent bladder tumor is intravesical instillation of BCG. The expression of IL-2 is necessary for the success of the BCG immunotherapy. (Kaempfer & Shapiro JCO June 1966).

### The treatment of bladder cancer with a combination of BCG and IL2

Using IL-2 along with an intravesical instillation of BCG has been shown to be successful when treating superficial bladder cancer along with BCG. We propose to find out whether the addition of IL-2 to BCG treatments will convert patients that would fail the traditional BCG treatment to responders of the combined treatment. A phase I study was undertaken to assess the toxicity of the intravesical application of IL-2 to the bladder in concentrations ranging from 6 million units to 54 million units per treatment in conjunction with standard BCG (Tice or Connaught). Due to the considerable time involved with patient recruitment, phase II studies were done in conjunction with the phase I work. All 19 patients completed the Phase I study and all patients participated during the follow-up period. In the Phase I study, there were 20 reports of a fever higher than 38 degrees centigrade that lasted from 1-3 days in 10 patients. They did not need any medications for this side effect and it did not prevent them from completing the study (table 1). One patient had severe arthralgia and fever 3 weeks after the last (6th) treatment and was treated with dual anti-tuberculosis medication and later by 3 Hydrocortisone injections. The response to the treatment was a complete recovery from the arthralgia. The blood tests for urea, electrolytes, liver and thyroid were all in the normal range during the treatment and follow-up periods. The cytology test for bladder cancer was negative before, during and after treatment. Cystoscopy performed after the initial treatment at months: 3, 6, 9, 12, 16, 20, 24 and 30 were all free of tumors except for 3 patients. The recurrence happened in 1-3 years and all the patients did not quit smoking. The bladder was a bit red as observed following BCG treatment. 18

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