Management of patients with non muscle invasive bladder cancer. Comparative study of different therapeutic approaches.

Abstract

Introduction

Bladder cancer is a common pathology that requires a complex management. Bladder cancer is divided into non muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer. Even if at diagnosis about 75% of patients are with non muscle invasive bladder cancer during the course of the disease many of them have recurrence and even get to present tumor progression.

This thesis addresses the multiple aspects of the management of non muscle invasive bladder cancer patients, from etiology such as associating a viral inductor factor (infection with human papilloma virus HPV) to aspects of correct classification of patients and the management of the follow-up from diagnosis to recurrence and disease progression.

Hypothesis and Aim

NMIBC is a pathology intensively studied in recent years, however researchers worldwide are seeking new ways to improve the management of patients with NMIBC. The aim of the thesis was to assess an individual management for each patient through the finding from the studies conducted.

Material and Methods

The methodology of the thesis included 4 studies:

1. a retrospective study with long term follow-up of the patients with NMIBC treated with trans urethral resection of bladder (TUR-B) or TUR-B plus Bacillus Calmete Guerin (BCG) intravesical instillations in Mures County Hospital at the Urology Department, aim of the study was to validate the EORTC scores and to compare oncological outcomes between the groups.

2. a prospective series of patients with single lateral bladder wall muscle invasive bladder cancer treated with Radical Cystectomy (RC) and Pelvin Lymph Node Dissection (PLND), aim of the study was to observe the overall survival and to find a correlation between controlateral lymph nodes before surgery and after surgery.

3. a prospective randomized trial, that included 200 consecutive patients with MIBC, that undergone RC with extended PLND at the Urology Department in Inselspital, Bern, Switzerland. Patients were randomized in two groups of 100, first group were treated with re-adaptation of the dorsolateral peritoneal layer after RC with ePLND and in the second group the treatment was standard RC with ePLND without re-adaptation. The aim was to demonstrate the safety use of the re-adaptation in long term follow-up and the improvement in gastrointestinal function at 2 years after surgery.

4. a case-control study assessing the knowledge about HPV infection in a NMIBC patients cohort. Aim of the study was to observe the level of knowledge about HPV and to identify eventual risk factors for HPV infection.

Results

Results of the first study conducted demonstrated the importance of the EORTC score for stratifying NMIBC patients. Lowest recurrence free survival (RFS) rates were demonstrated at patients with recurrence EORTC scores between 5 to 9 and lower progression free survival (PFS) at patients with progression EORTC scores between 7 to

23. Better RFS and PFS were demonstrated at patients with TUR-B plus BCG intravesical instillations. Independent prognostic factors for recurrence were multiple tumors and EORTC score higher than 5, and for progression was EORTC score higher than 7. Statistical significant difference was observed between the mean EORTC scores at patients with recurrence/progression during follow-up than in the non-recurrence/progression patients ($p<0.001$).

Results of the second study showed a correlation Kappa of 0.63 between controlateral negative lymph nodes preoperatory at CT scans and controlateral negative lymph nodes postoperatory at histology reports. Also for T1/2 N0M0 patients overall survival during follow up was according to literature reports.

Third study results demonstrated no difference between groups in terms of overall survival, cancer specific survival and recurrence free survival; also fewer local recurrences were noticed than reported before in literature. In terms of gastrointestinal function after RC with ePLND, patients that benefit from re-adaptation of the dorsolateral peritoneum after RC with ePLND experienced less constipation at 2 years according to Gastrointestinal Quality of Life Index (GIQLI) validated questionnaire ($p<0.04$), also according to Bern institutional post Cystectomy follow-up questionnaire more patients that had re-adaptation reported a regular stool than in the non re-adaptation group at all follow-up time points ($p<0.0001$, 0.005, 0.005, 0.04 at 3, 9, 12 and 24 months respectively), similar results were shown regarding constipation and abdominal pain.

Forth study results demonstrated a low level of knowledge about HPV in NMIBC patients, but no statistically significant difference between NMIBC and controls. Risk factors that were reported for HPV infection before were identify in the NMIBC group such as: higher number of sexual partners and unprotected intercourse.

Conclusions

1. Management of patients with non muscle invasive bladder cancer should be based on individual characteristics.
2. Stratification of the patients' according to prognostic factors and EORTC scores is mandatory, and follow-up and management of the disease should be done accordingly.
3. For high risk patients with recurrence EORTC score higher than 5 and progression EORTC score higher than 7, intravesivcal instillations with BCG are mandatory, due to better oncological outcome.
4. Even with a good management there are patients at high risk that progress to MIBC.
5. MIBC patients should benefit of the re-adaptation of the dorsolateral peritoneal layer after RC with ePLND due to better gastrointestinal recovery.
6. PLND on the controlateral side for T1/2 N0M0 MIBC patients with single tumor located on the lateral bladder wall is oncological safe.