

Natural History, Treated Natural History and Prophylaxis of Non-muscle Invasive Bladder Cancer

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Urinary bladder cancer (BC) is the broad spectrum of disease ranging from low-risk to life-threatening high-risk. For the quality control of BC management, the natural and/or treated natural history of BC is the key for decision making of treatment strategy. It is well known that BC is caused by chemical carcinogenesis exogenously or endogenously, and nature of BC is categorized into two patterns, approximately 75% of them presents papillary non-muscle invasive nature, and 25% presents non-papillary muscle invasive nature. In experimental BC models induced by n-butyl-n-hydroxybutyl nitrosamine, rats develop only non-muscle invasive bladder cancer (NMIBC), and mice develop only carcinoma-in-situ (CIS) and MIBC, and both types of BC in dog. However, the mechanism why different types of BC developed in different species by same carcinogen is still uncertain.

To achieve better treatment strategy for NMIBC, it should be constituted with accurate clinical staging, complete TURBT, reliable pathological diagnosis and long-term follow-up protocol. The precise evaluation of clinical staging and biological malignancy of BC are key factors to make the long-term treatment strategy at the time of initial diagnosis. NMIBC has a good prognosis, but has multiple nature in terms of spatially and/or temporary recurrence. Frequent recurrence following TURBT may cause by non-visible small tumor(s) under standard cystoscopy. Progression of NMIBC mainly depends on its biological malignancy that cannot be detected under ordinary pathologic diagnosis.

For the multi-institutional clinical trial of chemoprophylaxis following TURBT, the evidence will be made in uniform condition. Minimally, the policy of TUR should be uniformed as to complete TURBT that includes complete resection of all visible tumors, secure resection of marginal tissue and certain resection of muscle layer under the tumor. If the specimen is not containing the muscle tissue, or is not suitable for pathological diagnosis, second TUR should be mandatory. Concerning to the accuracy of pathological diagnosis, local pathologists have a tendency of over diagnosis both in stage (Ta vs. T1) and grade (G1 vs. G2) when compared with that of expert uropathologist. However, it has a little influence on the clinical outcome of s-BT. The follow-up schedule is very important issue of chemoprophylaxis study, but it is the time to deserve a new look on the interval of cystoscopic examination. In our previous trial of SBT-003, it needed average 19.1 cystoscopic examination in control group and 44.1 in Epirubicin group to find one event of recurrence.

Many clinical trials using chemotherapeutic agents have been done in Nara Urologic Research and Treatment Group focusing on Epirubicin since 1990. It is concluded that the recurrence could be controlled during the instillation period, but recurrence were observed after discontinuation of intravesical chemotherapy. Despite the several degrees of adverse events, the main stream of prophylactic treatment following TURBT has been shifted from chemotherapeutic agents to BCG gradually. Intravesical BCG instillation seems to be effective for both treatment and prophylaxis against s-BT.

From Jan. 1985 to Dec. 2003, total 472 cases of s-BT were treated in Nara Medical University Hospital. Non recurrence survival rate at 5, 10 and 15year was 67%, 60% and 56% respectively. Progression-free survival rate at 5, 10 and 15year was 92%, 88% and 84% respectively. With the multivariate subgroup analysis, multiplicity and shape (peduncular/sessile) have significant impact on tumor recurrence, and grade (G1 versus G3) and shape have impact on tumor progression. Among 472 cases, 204 cases underwent TURBT alone. Non recurrence survival rate at 5, 10 and 15 years was 63%, 59% and 52% respectively. Progression-free survival rate 15year was 96%. With the multivariate subgroup analysis, only multiplicity has the impact on tumor recurrence in low-risk NMIBC.

From our data, the factor influencing on recurrence is tumor multiplicity, in other words, invisible mucosal lesions at the time of initial TURBT. The factor influencing on progression is tumor shape (sessile tumor), i.e. invisible submucosal lesions. Frankly, the former is caused by limitation of standard cystoscope, and is requiring novel photodynamic diagnosis (PDD). The latter is caused by limitation of standard pathology, and molecular makers available in clinics are anticipated in future.

Since 2006, PDD using 5-Aminoleuvlic acid (5-ALA) introduced to TURBT in NMU. TURBT with PDD is effective for prevention of overlook small and flat lesions, confirmation of complete resection and the detection of CIS. Preliminary result revealed that the sensitivity is 96%, and specificity 64% in 263 bladder specimens. The VTR of TUR under PDD will be presented.

In conclusion, s-BT is clearly categorized into two groups, low-risk and high-risk group, but initial treatment is the same, TURBT. The cystoscopic findings, such as solitary/multiple and peduncle/sessile, is the key point for decision making. The factors influencing on recurrence, progression and prognosis are depending upon the initial management based on the knowledge of treated natural history including prophylaxis, and the skill of complete TURBT.