

HEALTH RELATED QUALITY OF LIFE IN BLADDER CANCER. CURRENT APPROACH AND FUTURE PERSPECTIVES

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Abstract

Bladder cancer is a real health problem due to its increased incidence, high recurrence rate and the fact that usually it is detected in advanced stages with limited number of diagnostic tools and different therapy response rates to current therapeutic strategies. Because of these issues we must develop screening programs and sensitive diagnostic strategies capable of detecting the disease during its early stages but also for characterizing evolution, prognosis and therapeutic response. Issues of great importance are those related to health quality of life of patients from the moment of diagnosis till the use of existing therapeutic approaches. This paper reviews some facets of life quality in patients diagnosed with bladder cancer stressing upon some proposed questionnaires and some new cell and molecular biology and genomic acquisitions (molecular biomarkers) that may become indicators of prognosis, therapeutic response and life quality but also essential tools in guiding therapeutic strategies.

Keywords: quality of life, urinary bladderneoplasms, molecular biology, HRLQ questionnaire, molecular biomarkers

Introduction

Bladder cancer is one of the most commonly diagnosed malignant pathologies worldwide with increased incidence, prevalence and limited diagnostic tools for the early stages of bladder transitional carcinoma. Transitional

cell carcinoma is the most frequent histopathological type of bladder cancer followed by squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Bladder transitional carcinoma is also the most expensive oncologic pathology because of its increased incidence, high recurrence rate (50-80%), limited diagnostic tools and diagnostic challenges in the early stages [1]. Usual diagnostic tools used in clinical urology: cystoscopy and

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urine cytology provide positive diagnosis in 80% of clinical cases but frequently are not able to detect small tumors, flat tumors, “plaque-like” bladder carcinomas and in situ carcinomas where fluorescence cystoscopy will complete the positive diagnosis beside ELISA tests (BTA, NMP 22) and cytology based tests (ImmunoCyt, uCyt and UroVision) [2,3]. Molecular biomarkers might decrease false positive rates of photodynamic diagnostic techniques and provide early diagnosis of early stages in bladder malignancies using different genetic mutation (9q24.1deletion) or other chromosomal imbalances involved in bladder carcinogenesis [4]. Molecular biomarkers might provide early diagnosis of primary bladder tumors and tumoral recurrences, as well as therapeutic targets in developing precise therapeutic strategies according to molecular profile of bladder tumors. These biomarkers represent potential prognostic tools which might be used in non-invasive surveillance of patients who underwent cystectomy for bladder cancer [5,6].

Life quality assessment in patients diagnosed with bladder cancer is a complex qualitative and quantitative evaluation of global quality of life after positive diagnosis of bladder cancer which is dependent on the patient’s beliefs, life perception and expectation of each patient undergoing multiple cystoscopies, radical surgery, urinary reconstruction or urinary diversion surgery, radiotherapy or chemotherapy, but also dependent of clinical aspects of oncologic disorder: early diagnosis, therapy response, recurrence rate and related symptoms in bladder malignancies [7]. Functional transformation of all these subjective components (symptoms or clinical signs, cognitive profile of the oncologic patient, expectations and therapy response) to questions and numerical scores is a complex process in developing accurate and objective questionnaires validated by numerical scores which might provide a global evaluation of life quality in oncologic patients. Health related life quality questionnaires are applied in dynamics to evaluate life quality of oncological patients according to therapy response, type of treatment and personal capacity to accept positive diagnosis and treatment in bladder cancer. Clinical studies have revealed that urinary and sexual symptoms affect the most the quality of life in patients diagnosed with bladder cancer [7,8]. Different EORTC (European Organization for Research and Treatment of Cancer) and FACT (Functional Assessment of Cancer Therapy) questionnaires aim to evaluate quality of life, psychosocial and professional aspects after positive diagnostic of bladder malignancy. FACT BI, FACT VCI (FACT BI Cys), EORTC BLS24 and EORTC BLM30 are questionnaires which are applied for non-muscle invasive and muscle invasive bladder cancer respectively. Choosing one of these questionnaires in evaluating life quality of patients diagnosed with bladder cancer depends on the patient’s age, tumor grade, tumor stage, type of treatment, therapy response and associated comorbidities [6,7,9].

The aim of this current literature review is to identify if molecular biomarkers (miRNA, genetic polymorphisms, CNA) which are already validated as diagnostic or prognostic biomarkers in bladder cancer might be used as evaluation parameters in health related life quality questionnaires applied in bladder cancer patients: FACT G (Functional Assessment of Cancer Therapy) or EORTC (European Organization for Research and Treatment of Cancer). Using molecular biomarkers in bladder cancer pathology might provide early diagnosis of primary tumors and tumoral recurrences, non-invasive surveillance after surgery and precise therapeutic strategies according to molecular profile of bladder tumors. All these facts might significantly improve life quality of patients diagnosed with bladder cancer and propose molecular biomarkers as non-invasive diagnostic, prognostic, surveillance and screening tools in clinical practice.

Quality of life indicators, molecular biomarkers and health related quality of life questionnaires (HRLQ) scores

Molecular biomarkers involved in bladder carcinogenesis (miRNA, genetic polymorphisms, copy number alteration) might play an important role in prognostic evaluation of oncologic patients and some of these biomarkers are correlated with survival rates, therapy response and clinical outcome. Using these molecular biomarkers in clinical practice might increase the quality of life by decreasing recurrence rate and providing minimal invasive surveillance tools after radical cystectomy [10]. MicroRNA-141,-200c and -miRNA-121 are up regulated in bladder cancer, while miRNA-145, -125,-199a,-7c,-100 are down regulated in bladder malignant pathology [11,12] and might become part of a prognostic scale defining clinical outcome of bladder cancer patients or part of health related life quality questionnaires [13]. MiRNA 486-3p and 103-3p are correlated with overall survival rates in patients with bladder malignant tumors [14].

There is no single questionnaire for life quality assessment in patients diagnosed with bladder cancer. Prospective clinical studies try to constantly improve health related life quality questionnaires (HRQL) for oncological patients. Molecular biomarkers might significantly improve life quality providing early diagnostic, precise therapy and non-invasive surveillance tools. They may significantly decrease recurrence rate of bladder malignant tumors. Health related life quality questionnaires are dynamic tools, they try to improve constantly and define specific aspects of patients diagnosed with malignant tumors. Prospective clinical studies must validate most reliable genetic biomarkers which might be used as diagnostic or prognostic tools in clinical practice of patients diagnosed with bladder malignancies. Molecular biomarkers validated by clinical studies might become parameters for HRLQ questionnaires.

Health related life quality questionnaires can be generic or specific, adapted to different oncologic pathology and aim to provide a quantification of life quality in patients diagnosed with oncologic disorders before and after surgical treatment, radiotherapy and chemotherapy [7,14]. They must be able to measure therapy response rate and specify emotional, social and professional impact in patients' life.

Health related life quality (HRLQ) questionnaires

EORTC (European Organization for Research and Treatment of Cancer) health related quality of life questionnaires are applied before and after positive diagnosis of malignant bladder tumors, before and after surgical treatment, and are defined as dynamic prospective clinical studies in evaluating life quality of patients diagnosed with bladder cancer. EORTC QLQ C30 is a questionnaire applied in patients who underwent multiple cystoscopies for positive diagnosis of bladder tumors based on 30 questions grouped in 5 functional scales (physical, role, emotional, cognitive and social) and 3 symptoms scales (pain, fatigue, nausea and vomiting) and a few additional symptoms in evaluating global health status (insomnia, loss of appetite, constipation, diarrhea) [15]. The most common limitations of these questionnaires are represented by questions selection and objective quantification of clinical symptoms, geriatric patients evaluation, female patients diagnosed with bladder malignant tumors, recurrence rate of malignant tumors in preserved bladder tissue, type of surgery (minimal invasive surgery versus radical cystectomy with or without bladder reconstruction) [16].

EORTC QLQ C30 questionnaire has three different versions and life quality scores provided by this questionnaire ranges between 0-100. High score for functional scale means high level of functioning and health of patients, high score for global health status is translated to high quality of life in patients diagnosed with bladder cancer, and high score for symptoms scale means high level of symptomatology and poor clinical outcome, high side effects or low therapy response rate [17,18].

EORTC QLQNMIBC C24 is a health related life quality questionnaire for patients diagnosed with non-muscle invasive bladder tumors which evaluates psychometric properties in these patients regarding urinary symptoms, intra-vesical treatment compliance, sexual function and dysfunction, sexual intimacy and enjoyment [19]. EORTC QLQ NMIBC C24 questionnaire score is highly related with EORTC QLQ C30 score but is adapted to early stages of bladder cancer (Ta, Tis, T1). EORTC QLQ BLM 30 questionnaire is assessing urinary and bowel symptoms, sexual dysfunction through 30 questions adapted to patients diagnosed with T2, T3a, T4b bladder tumors [20].

FACT (Functional Assessment of Cancer Therapy)

questionnaires evaluating quality of life of oncologic patients are based on FACT G domains: physical, social, family and emotional well-being and functional well-being and additional items according to specific malignant pathology. FACT BI (Functional Assessment of Cancer Therapy in Bladder cancer) is a health related life quality questionnaire that evaluates life quality of patients diagnosed with bladder malignancies by assessing 5 groups of global health (FACT G domains): physical, social, family and emotional well-being, emotional, functional well-being and 13 related items regarding urinary tract and intestinal symptoms, sexual disorders, stoma concerns after cystectomy and body image concerns [21-23]. FACT BI is a useful tool along with EORTC questionnaires in the quantification of life quality of patients diagnosed with bladder cancer [24]. FACT BI scoring procedure is a multifactorial process dependent on surgery type, urinary diversion chosen for these patients, therapy response and emotional status which is mainly dominated by anxiety and social well-being after bladder cancer surgical treatment [24,25]. FACT BI questionnaire provides more accurate evaluation of life quality of oncological patients diagnosed with bladder cancer than EORTC QLQ C30, which might be applied for various type of malignant tumors but has a reduced sensitivity in bladder cancer. FACT BI score is also dependent on cultural background, health educational level in understanding pathological status derived from positive diagnosis of bladder malignancy and capacity of controlling emotional and cognitive status after positive diagnosis of bladder cancer [26,27].

Quality of life and survival rates are the main characteristics which define psychological, functional and cognitive profile of patients diagnosed with bladder cancer beside urogenital, sexual and family concerns. Defining molecular profile of bladder malignancies will constantly improve clinical outcome and quality of life in these patients by providing early diagnostic and therapeutic options according to molecular profile of bladder tumors. Multiple questionnaires are available in evaluating quality of life in patients diagnosed with bladder cancer: EORTC, BCI (Bladder Cancer Index) or FACT BI or FACT VCI. Mainly, good global health, sexual function and active family relationship are defining life quality in patients diagnosed with bladder malignancies, while anxiety, functional or social/family well-being parameters are improving in time after radical cystectomy [26,27].

FACT VCI (Vanderbilt Cystectomy Index) known as FACT BI Cys questionnaire is a health related quality of life evaluation for patients diagnosed with bladder cancer who underwent radical cystectomy and urinary diversion based on FACT G main domains and 17 related items regarding sexual and urinary functions, body image and stoma concerns [4,15,27]. Quality of life evaluated by FACT VCI questionnaire revealed that uretero-cutaneostomy in patients diagnosed with bladder cancer is associated with

better quality of life [16,28].

BCI (Bladder Cancer Index) is a multidimensional, complex tool for the evaluation of health related quality of life in patients diagnosed with bladder cancer who underwent local therapy. BCI questionnaire includes 36 questions assessing urinary, sexual and bowel symptoms and global health. BCI score has significant differences depending on type of cystectomy or endoscopic based procedures. Urinary function score was lower for patients treated with continent bladder versus ileal conduit [17,21,29,30].

Assessment of health related quality of life in patients diagnosed with bladder cancer using Functional Assessment of Cancer Therapy (FACT) or European Organization for Research and Treatment of Cancer (EORTC) questionnaires, revealed that life quality of these patients depends on age, associated comorbidities, surgery type, type of treatment (radical cystectomy or preservation therapy), urinary diversion type, and that sexual dysfunction have high impact on the quality of life in these patients above other related symptoms of oncologic disorder or body image aspects [18,31]. Evaluation of life quality in patients over 75 years old with associated co morbidities show that cutaneous ureterostomy is correlated with better quality of life than radical cystectomy. Sexual dysfunction and erectile disorders after radical cystectomy mainly

affects the quality of life in patients diagnosed with bladder malignant tumors in comparison with urinary diversions [32,33,34].

Nerve sparing cystectomy might improve quality of life by avoiding sexual dysfunctions. Radical cystectomy does not affect significantly life quality in these patients, but urinary diversion has great impact by associating sexual dysfunctions, so patients diagnosed with bladder cancer have a better global health status according to chosen therapeutic option [35]. The therapeutic options for patients diagnosed with bladder malignant tumors also have a high impact on quality of life. Transurethral resection of bladder tumors (TUR BT) followed by chemotherapy associates lower quality of life when compared with radical cystectomy [36,37]. Precise therapy according to molecular profile of tumors might significantly improve quality of life and minimize side effects of current therapeutic options. TURBT (transurethral resection of bladder tumors) for non-muscle invasive bladder cancer is correlated with better clinical outcomes and quality of life and low risk of early recurrence [38]. These findings reveal the importance of early diagnosis in bladder tumors and importance of molecular biomarkers (microRNA, genetic mutations) in developing early diagnostic strategies and precise therapy according to molecular profile of bladder tumors [39,40].

Table I. Quality of life questionnaires in bladder cancer [15-34].

HRQL Questionnaires	Evaluation criteria
EORTC QLQ C 30	Sexual function, bowel symptoms, urostomy/catheter concerns, body image concern
EORTC QLQ NMIBC C24	Urinary symptoms, intra-vesical treatment tolerance, sexual function, sexual intimacy, sexual enjoyment, bowel disorders (bloating, flatulence)
EORTC QLQ BLM30	Urinary symptoms, bowel symptoms, sexual function, stoma/catheter concerns, body image concerns
FACT G (general)	FACT G (general) domain asses physical, social/ family, emotional and functional well being
FACT BI	FACT G (general) domain +13 additional items regarding bowel function, sexual interest, body image concern and stoma concern
FACT VCI	FACT G (general) domain +17 additional items regarding sexual and urinary function, body image concern
BCI (Bladder Cancer Index)	Bowel function, urinary and sexual function and related symptoms to these categories

Discussion and Conclusions

Molecular biomarkers might provide early diagnosis of primary bladder tumors and tumoral recurrence and therapeutic targets for developing precise therapeutic strategies according to the molecular profile of bladder cancer. Molecular biomarkers might be proposed as diagnostic, prognostic or therapeutic tools in clinical practice of patients diagnosed with bladder cancer or potential parameters included in screening programs or HRLQ questionnaires. Main differences induced by using molecular biomarkers in health related life quality questionnaires might be revealed by clinical parameters like: number of tumoral bladder recurrences and its early diagnostic, patients' compliance (measured by financial costs, hospitalization time, social and professional reintegration after positive diagnostic) reported symptoms during diagnostic evaluation and after surgical treatment (pain, urinary /sexual dysfunction, body image evaluation associated to current tools versus novel molecular diagnostic and prognostic tools) ADL level (activities of daily living level after positive diagnosis of bladder cancer) and therapy response rate. Important parameters in life quality evaluation is represented by social and professional reintegration after bladder cancer diagnosis, social enjoyment, family support and communication after positive diagnosis of oncologic disorder. Significant differences between current clinical tools (cystoscopy, histopathological examination) and molecular biomarkers might be revealed by survival rates and life quality level especially by decreasing the number of tumoral recurrences and non-invasive surveillance after cystectomy. The limits of introducing molecular biomarkers in current clinical practice of bladder cancer and life quality questionnaires are represented by clinical validation of these biomarkers in urologic clinical practice through prospective clinical studies and costs of applying these biomarkers in current clinical practice in patients diagnosed with bladder cancer.

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