

กลุ่มอาการในผู้ป่วยมะเร็งกระเพาะปัสสาวะ: การวิเคราะห์ทุติยภูมิ

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Symptom Clusters in Patients with Bladder Cancer: A Secondary Analysis

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หลักการและวัตถุประสงค์: ผู้ป่วยมะเร็งมักประสบกับอาการหลายอาการที่เรียกว่ากลุ่มอาการอันเป็นผลจากโรคและวิธีการรักษา การศึกษาเกี่ยวกับกลุ่มอาการอาจนำไปสู่การจัดการที่มีประสิทธิภาพให้กับผู้ป่วยที่ต้องทุกข์ทรมานจากอาการต่างๆ ดังกล่าวได้ การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษากลุ่มอาการในผู้ป่วยมะเร็งกระเพาะปัสสาวะชาวไทย

วิธีการศึกษา: เป็นการวิเคราะห์ทุติยภูมิจากข้อมูลผู้ป่วยมะเร็งกระเพาะปัสสาวะที่เข้ารับการรักษา ณ หน่วยตรวจระบบทางเดินปัสสาวะ โรงพยาบาลมหาวิทยาลัยแห่งหนึ่งในประเทศไทย จำนวน 62 ราย

ผลการศึกษา: กลุ่มตัวอย่างส่วนใหญ่ร้อยละ 40.3 เป็นผู้ที่มาตามนัดหลังสิ้นสุดการรักษาระยะที่มารักษาด้วยการฉีด BCG เข้าในกระเพาะปัสสาวะร้อยละ 27.4 เคมีบำบัดร้อยละ 21.0 และรังสีบำบัดร้อยละ 11.3 กลุ่มอาการที่พบประกอบด้วย กลุ่มอาการที่หนึ่ง: ท้องเสีย เบื่ออาหาร นอนไม่หลับและอ่อนล้า กลุ่มอาการที่สอง: ท้องผูก ปวดหลัง และกลุ่มอาการที่สาม: ปัสสาวะบ่อยและแผลในปาก/คอ

สรุป: ความรู้ที่ได้จากผลการศึกษานี้จะเป็นประโยชน์สำหรับบุคลากรด้านสุขภาพที่จะคำนึงถึงกลุ่มของอาการที่เกิดขึ้นในผู้ป่วยมะเร็งกระเพาะปัสสาวะ และสามารถนำไปวางแผนจัดการกับอาการที่เกิดขึ้นได้อย่างมีประสิทธิภาพต่อไป

คำสำคัญ: มะเร็งกระเพาะปัสสาวะ, กลุ่มอาการ, การจัดการอาการ

Background and Objective: Patients with cancer often have experience of multiple symptoms, which are called symptom clusters, due to the consequence of disease or treatment. Study of symptom clusters may lead to effective management in patients suffering from such symptoms. The aim of this study was to explore the symptom clusters in Thai patients with bladder cancer.

Methods: A secondary analysis of sixty-two bladder cancer patients attending a urology clinic at a Thailand university hospital was done to determine the clustering of symptoms.

Results: The majority of participants came to hospital for follow-up appointment after complete course of treatment (40.3%), BCG intravesical therapy (27.4%), chemotherapy (21.0%), and radiotherapy (11.3%). Three distinct symptom clusters were identified. First cluster: diarrhea, lack of appetite, sleep disturbance, and fatigue; second cluster: constipation, back pain; and third cluster: frequent urination, and mouth/throat sores.

Conclusion: This study can provide beneficial information for health professionals to consider about clustering symptoms of patients with bladder cancer, and could plan for symptom management more effectively.

Keywords: Bladder cancer, Symptom clusters, Symptom management

สรินกรินทร์เวชสาร 2561; 33(5): 431-7. • Srinagarind Med J 2018; 33(5): 431-7.

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Introduction

Bladder cancer (BCa) is one of the most widespread cancer and is ranked number nine among common malignancies existing in the world¹. It has the highest incidence in North America and Europe². BCa commonly occurs in men compared to women, approximately three folds. Each year, there are 4.4 patients per 100,000 who were death from BCa worldwide. Prognosis of patients with BCa was variable, ranging from mild disease with a low mortality rate to extremely high-grade tumors associating with high mortality³. In Thailand, BCa is the fifth most common type of cancer in men and the ninth in women with the incidence of 4.2 and 1.3 new cases per 100,000 in men and women, respectively⁴.

BCa typically begins in the bladder inner layer wall then extends to the outer lining, and metastasizes to other areas. The staging and grading of tumors have been recognized as important indicators of prognosis, survival, and therapeutic response for BCa. Additionally, there is a strong correlation between both staging and grading. Tumor stage is used to describe how far the tumor has invaded into the bladder walls. Tumor grades are referred to the potential for disease progression and recurrence⁵. High grade tumors are most likely to progress and carry worse prognosis⁶. Unfortunately, about 70% of patients with BCa have tumor recurrence and BCa patients possibly experience tumor recurrence at least once during the follow-up period⁷.

The majority of patients with BCa experienced multiple symptoms that occur in groups or clusters, stemming from the disease and treatment consequence throughout the illness duration. For example, patients often had abdominal, pelvic or back pain and bowel movement problems relating to the spreading of cancer cells through tissue layers of the bladder⁸. In advanced BCa, the symptoms included fatigue and weight loss⁶.

In addition, findings from previous studies in Thailand and other countries revealed that BCa treatments also caused additional symptoms such as nausea, vomiting, mouth/throat sores, body itchiness, diarrhea, constipation, and burning sensation in the bladder^{9,10}. Whereas BCG treatment has high incidence

of bladder irritation, general malaise, and fever, mouth/throat sores^{11,12}.

Currently, there is no reported study about BCa survivors' symptoms, however; for a prospective follow-up study of Goedendorp and colleague¹³, they found that some BCa patients included in the study were research participants and the results revealed that BCa survivors had severe persistent fatigue, impaired sleep and had to take a rest over the last six months in the first year after cancer treatment.

The theory of unpleasant symptoms (TOUS) was used to guide for this study. TOUS has three major components, which include the symptoms that the patient experienced during having BCa, the influencing factors that affected those symptoms, and the negative outcomes associating with those symptoms. The theory emphasized that the symptom experience of BCa patients had various symptoms, which can occur concurrently, therefore; patients seldom had single symptom in isolation. Symptoms of those patients are multidimensional and could include perceptions of prevalence and severity¹⁴.

Symptom clusters (SCs), groups of two or more symptoms that occur simultaneously, may be independent from other SCs, and may or may not have a common etiology or underlying mechanism similarly to other SCs¹⁵. Symptoms within the same cluster tended to intensify each other¹⁶. For example, for the symptom cluster of pain, fatigue, and *nausea*, fatigue and nausea often intensified pain¹⁴. Additionally, for the symptom cluster of pain, fatigue and *depression*, pain causing fatigue normally led to less pain tolerance and depression¹⁷. Consequently, the presence of multiple concomitant symptoms often adversely affected physical, emotional, social, and spiritual functional status of patients and these led to reduced quality of life^{18,19}. Ignoring symptom clusters may threaten important patient health outcomes²⁰.

Although researchers had studied symptom clusters in various types of cancer (e.g. breast, prostate, lung, liver, colorectal, head and neck^{21,22}), there is currently no published studies on symptom clusters, which is specific to patients with BCa. The aim of this

study is to explore symptom clusters in Thai patients with BCa.

Methods

Study design: This study was a secondary analysis study. Following the ethical approval by the research institutional review boards, the data were collected from a cross-sectional study of symptom management in patients with BCa¹⁰.

Participants: Participants included in the primary study were patients, who were diagnosed BCa by a physician, and attended a urology clinic of the university hospital between December 2011 and June 2012. For this study, all data obtained from the BCa patients were analysed with no further inclusion or exclusion criteria.

Instrument: The primary research instrument is a questionnaire developed by the investigators from relevant literatures which consists of Part 1: Demographic data including gender, age, marital status, religion, and education, Part 2: Reasons for hospital visits, health history, and grades of cancer, Part 3: Information relating to the symptoms, frequency and severity, and Part 4: Information relating to symptom management and treatment outcomes. This questionnaire also included open-ended questions about the patients' symptom management strategies. However, only part 1-3 were analyzed for this study.

Data collection: After completing informed consent, participants completed the symptom questionnaires. Information of diagnosis, reasons for hospital visits, health history, and grades of cancer were obtained from patient records.

Data analysis: Samples and symptom characteristics were described using means and standard deviations for continuous variables whereas frequencies and percentage were presented for categorical variables. Symptom clusters were analyzed by factor analysis via a principle component analysis and simplified by the varimax rotation. The eigenvalue was set at 1.0 and it was concerned as a factor loading number when the value was greater than 0.4, exclusively used for this research. For the generated factors, only those, which

was significant in correlation, were accepted. Potential symptom clusters were also required to be non-overlapping.

Results

Participants' characteristics: In total, 62 patients participated in this study. As shown in Table 1 mostly were males (77.4%) and had age between 45-78 years old (median=68); married status (66.1%); Buddhist religion (96.8%); and a primary school education level (51.6%). The majority of patients came to the hospital for follow-up appointments (40.3%), BCG intravesical therapy (27.4%), chemotherapy (21.0%) and radiotherapy (11.3%). Most patients did not present with urinary system problems (69.4%). The majority of patients (59.7%) were diagnosed high grade cancers.

Table 1 Participants' characteristics (n=62)

Characteristics	n (%)
Gender	
Female	14 (22.6)
Male	48 (77.4)
Age	
Mean (SD)	59.8 (9.8)
Range	45-78
Marital status	
Married	41 (66.1)
Unmarried/divorced/widowed	21 (33.9)
Religion	
Buddhist	60 (96.8)
Other	2 (3.2)
Education	
Primary school	32 (51.6)
Secondary school	22 (35.5)
College or more	8 (12.9)
Reason to visit hospital	
Surveillance appointment	25 (40.3)
BCG intravesical therapy	17 (27.4)
Chemotherapy	13 (21.0)
Radiotherapy	7 (11.3)
Health History	
Smoking	39 (62.9)
Drinking	38 (61.3)
Urinary system problems	19 (30.6)
UTI	15 (24.2)
Calculi	4 (6.5)
Cancer Grade	
High	37 (59.7)
Low	25 (40.3)

Symptoms prevalence and severity: Symptoms were considered to be significant when patients rated the severity of symptoms greater than 0 in the Part 3 of questionnaire. Symptom prevalence and severity are shown in Table 2. The highest prevalence of symptoms were back pain (51.6%) followed by fatigue (43.6%) and lack of appetite (37.1%).

The most severe symptom was back pain (mean=5.2, SD=1.9), followed by mouth/throat sores (mean=4.9, SD=2.5). Whilst, the least severe symptom was diarrhea (mean=3.1, SD=1.0), followed by fatigue (mean=3.6, SD=1.6). Most of patients (74.2%) experienced multiple symptoms having two or more symptoms and 8.1% of patients did not experience any symptoms at all.

Table 2 Symptom prevalence and severity (n=62)

Symptom	Prevalence		Severity*	
	n	%	Mean	S.D.
Back pain	32	51.61	5.23	1.93
Fatigue	27	43.55	3.61	1.58
Lack of appetite	23	37.10	3.97	1.89
Frequent urination	22	35.48	4.00	1.66
Constipation	21	33.87	3.83	1.40
Sleep disturbance	18	29.03	3.81	1.69
Anxiety	14	22.58	3.70	1.49
Mouth/throat sores	12	19.35	4.93	2.49
Diarrhea	10	16.13	3.08	0.99
Total symptoms				
No symptoms	5	8.07		
One symptom	11	17.74		
Two or more	46	74.19		

* Score 0-10

Table 3 Factor matrix[†] with Component Loading Factors (n=62)

Symptoms	Cluster 1	Cluster 2	Cluster 3	Cluster 4 (rejected)
1. diarrhea	.794			
2. lack of appetite	.749	.316		
3. sleep disturbance	.649			
4. fatigue	.568	.333		
5. constipation		.846		
6. back pain		.714		
7. frequent urination			.803	
8. mouth/throat sores			-.573	.425
9. anxiety				.920
% of variance explained	27.447	16.034	12.706	11.667
Total variance explained				67.854
Cronbach's alpha	0.82	0.72	0.81	-

[†] Principal components analysis with varimax rotation

Note: Cluster 1 = (diarrhea, lack of appetite, sleep disturbance, and fatigue);

Cluster 2 = (constipation, back pain);

Cluster 3 = (frequent urination, mouth/throat sores).

Symptom clusters: Four symptom clusters were identified with 67.9% of total variance explained. However, three of these clusters (1, 2, and 3) were significant in the additional criteria (see Table 3). Four symptoms (diarrhea, lack of appetite, sleep disturbance, and fatigue) were loaded on cluster 1 which explained 27.5% of the factor's variance. Cronbach's alpha coefficient was 0.82 and this indicated that these symptoms within the cluster occurred at a high rate with a homogenous pattern. Two symptoms (constipation and back pain) were loaded on cluster 2 explained 16.0% of the variance. The second coefficient was still high at 0.72 indicating a homogenous form. In addition, two symptoms (frequent urination and mouth/throat sores) were loaded on cluster 3 explained 12.7% of the variance. The third coefficient was 0.81 and this was once again in a homogenous formation. Cluster 4 was rejected on the basis of the overlapping with mouth/throat sores' symptoms of cluster 3. In addition, the loading score of mouth/throat sores in cluster 3 was higher than cluster 4. Consequently, cluster 4 was eliminated. Thus, final symptom clusters were cluster 1 (diarrhea, lack of appetite, sleep disturbance, and fatigue), cluster 2 (constipation and back pain) and cluster 3 (frequent urination and mouth/throat sores).

Discussion

For the clusters generated by the factor analysis, cluster 1 is comprised of diarrhea, lack of appetite, sleep disturbance, and fatigue symptoms. Possibly, these symptoms (loss of appetite, sleep disturbance, and fatigue) were recognized easily in both cancer patients and cancer survivors, especially in advanced stages or high grades of disease^{9,13,23,24}. Obviously, the majority of studies provided evidence supporting a strong correlation between fatigue and sleep disturbance which may be related to disease and treatment-induced abnormalities in cytokine-based etiology. Understanding that cytokines produce a collection of symptoms and behavioral signs when given to both humans and animal^{25,26}. In addition, symptom clusters had been studied by other authors

and it was found that a lack of appetite, sleep disturbance, and fatigue were clustered together²⁷.

Similarly, diarrhea is a common symptom in cancer patients, which was commonly found through cancer's trajectory²⁸. Intense psychological and emotional states, such as stress and anxiety in cancer, can trigger chemical changes that lead to increased intestinal permeability, bacteria can translocate across the mucosal lining and interfere bowel movements explained by the brain-gut connection concept²⁹. From literature reviews, this cluster of four symptoms may be caused by the effects of treatments, especially chemotherapy. Approximately 70-100% of cancer patients experienced fatigue after receiving treatment⁹ and this fatigue often persisted for a long period of time after treatment cessation³⁰. In a recent study of cancer-related symptom clusters, Skerman, Yates, and Battistutta³¹ found that sleep disturbance and fatigue were the most prevalent distressing symptom persisting in patients after commencing adjuvant chemotherapy.

In patients receiving chemotherapy, diarrhea can occur in 50-80% of treated patients depending on the chemical agents³². Cytotoxic chemotherapy affects the colonic crypt stem cells. Death of these cells leads to a cascading effect, whereby immature crypt cells attempt to compensate by releasing more secretory compounds. Additionally, these changes associated with destroying carbohydrate digestion and protein enzymes causing more secretion from the intestinal wall³³. Furthermore, these effects may cause a taste sensitivity deficit leading to appetite loss at the end³⁴.

In this study, most of the participants (40.3%) attended to the hospital for follow-up appointments as survivors after medical treatment completion. However, psychological and emotional sequelae can persist or periodically arise in some survivors. For example, cancer surveillance appointments can prompt marked fear of cancer recurrence³⁵. Additionally, receiving intravesical BCG treatments can induce different side effects of those symptoms in cluster 1.

The symptoms in cluster 2 (constipation and back pain) associated with specific disease-related symptoms.

For constipation, which was ranked number five of the highest frequency in severity among the sample group, it is possible that cancerous tumors had spread from the bladder and compressed the intestines; consequently, this caused difficulty in eliminating intestinal content. Additionally, the stress of illness could have reduced appetite and food consumption, resulting in less bowel content. Back pain, another symptom in this cluster, was also the most prevalent and most severe symptom in the patients. This finding is consistent with previous study by cancer organizations and they found that back pain was the dominant complaint in patients with advanced BCa⁹.

Cluster 3 symptoms (frequent urination, mouth/throat sores) associated with consequence of the treatments. Although side effects of intravesical BCG therapy are rare, cystitis with symptoms of urinary frequency is the most prevailing urinary complication¹². Symptoms of mouth/throat sores may be a side effect of chemotherapy occurring in patients receiving chemotherapy treatment, approximately 21%.

Although a major strength of this study was the identification of symptom clusters, which was focused on patients with BCa, several limitations are needed to be considered. The sample size was relatively small and did not allow for separated evaluations of treatment-related symptom clusters in BCa patients, especially in patients who received surgery. In addition, the cross-sectional design was only a snapshot study. Symptoms of patients may improve or deteriorate over time along the disease and treatment trajectory. Additionally, further study is warranted to determine whether the symptoms in each cluster will still aggregate over time.

Conclusion

The findings of this study suggested that patients with BCa experienced three symptom clusters: diarrhea-lack of appetite-sleep disturbance-fatigue, constipation-back pain, frequent urination-mouth/throat sores. These symptom clusters should be explored further in future longitudinal studies with larger samples

and additional research should focus on designing effective interventions to reduce symptom burden from these clusters.

Acknowledgements

This study was supported by grants from the Faculty of Nursing, Chiang Mai University, Thailand. The authors declare no conflicts of interest. They thank all the patients who participated in this study. Additionally, their sincere gratitude is expressed to Professor Audrey Zenner, Academic Center for Excellence, University of Illinois at Chicago, Illinois, U.S.A. for an excellent review of the manuscript.

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