Int J Clin Exp Med 2019;12(9):11520-11528
www.ijcem.com /ISSN:1940-5901/IJCEM0097537

Original Article

Analysis of illness uncertainty and the related factors in patients undergoing heart valve surgeries during the perioperative period

Xue Wei[1], Xinlan Zhang[2], Xiaoyan Zheng[2], Lihua Zhou[1]

[1]College of Nursing, Anhui Medical University, Hefei, Anhui Province, China; [2]Department of Cardiovascular Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China

Received May 26, 2019; Accepted August 5, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Objective: This study was designed to explore the uncertainty in illness during the perioperative period for patients undergoing heart valve surgeries and analyze the related factors. Methods: A total of 162 patients who have received heart valve surgeries were selected as subjects. General information investigation scale, self-efficacy evaluation scale, medical coping modes questionnaire and Connor-Davidson resilience scale were used to gather relevant information before operation, while Mishel uncertainty in illness scale (MUIS) was used one day before operation and one day before hospital discharge to assess the level of illness uncertainty in patients and analyze relevant influential factors. Results: The scores of ambiguity, complexity, deficit information and unpredictability and total MUIS score for patients one day before hospital discharge were significantly lower than those for patients one day before operation ($P<0.001$). Age, years of education, average monthly family income, marital status, number of heart valve surgeries, complications and self-efficacy had significant effects on patients' perception of uncertainty in illness before operation ($P<0.05$). Pearson correlation analysis showed that there was a significant negative correlation between the total MUIS score one day before operation and resilience, self-reliance, optimism, confrontation, resignation, utilization of support, objective support and total social support ($P<0.05$), and there was a significant positive correlation between the total MUIS score and avoidance ($P<0.05$). Multivariate logistic regression analysis showed that age, years of education, number of heart valve surgeries, monthly family income, self-reliance, optimism, confrontation and resignation were important risk factors for illness uncertainty in patients before operation ($P<0.05$). Conclusion: The illness uncertainty felt by patients undergoing heart valve surgeries is at a medium level. Age, education background, number of heart valve surgeries, monthly family income, psychological resilience and coping modes are main factors affecting illness uncertainty in patients.

Keywords: Heart valve surgery, perioperative period, illness uncertainty, related factors

Introduction

Valvular heart disease is a common type of heart disease in China. It is caused by the cardiac function impairment induced by dysfunction of blood circulation, leading to the dysfunction of multiple organs including the liver, kidneys, digestive system and respiratory system, and even organ infarction [1]. At present, heart valve surgery has become one of the best treatments for severe thickening, malformation and limited movement of heart valves [2]. Surgery, as a traumatic stressor, can bring a variety of discomforts to patients' body and mind. When patients are in a state of anxiety, tension and fear during the perioperative period, the central nervous system can affect the body's endocrine system, resulting in elevated blood pressure, heart rate and respiratory rate. Serious negative mentality during the perioperative period can directly affect the efficacy of the surgery and lead to perioperative complications [3, 4].

Illness uncertainty is defined as the lack of ability to distinguish illness-related events and is regarded as a cognitive feeling or cognitive state by some scholars; it is thought to come along with the symptoms, diagnosis, treatment and prognosis of illnesses [5]. Illness uncertain-

ty refers to the shift from uncertainty to ambiguity in the cognitive process, which will change over time, and at the same time, this cognitive change process is accompanied by positive or negative emotional states [6]. A number of studies have shown that illness uncertainty can affect patients' psychological adjustment ability and coping ability, put patients under increasing stress, pose an obstacle to patients' perioperative rehabilitation, and reduce patients' quality of life [7]. This study explored illness uncertainty in patients undergoing heart valve surgeries, and analyzed the factors affecting illness uncertainty during the perioperative period, so as to provide a basis for formulating intervention strategies to reduce the level of illness uncertainty.

Materials and methods

Patients

A total of 162 patients who received heart valve surgeries in our hospital from June 2015 to June 2017 were studied, including 92 males and 70 females. All patients were between 22 and 68 years old, with an average age of 50.2±8.3. This study was approved by the Ethics Committee of College of Nursing, Anhui Medical University. All patients and their family members in this study signed the consent forms.

Inclusion criterion

The patient was more than 18 years old; the patient received heart valve surgery for the first time; the patient had the ability to communicate and could successfully complete the questionnaires of this study.

Exclusion criterion

Patients with mental disorders; patients with severe communication disorders; patients with malignant tumors, immune system diseases, hematopoietic system diseases or other severe diseases; patients with severe heart diseases, such as congenital heart disease, coronary heart disease, pulmonary heart disease, etc.

Survey tools

General information survey: Patients completed a general information questionnaire designed by our hospital one day before operation. General information including patients' gender, age, years of education, marital status, average monthly family income, ways of medical payment, type of valvular heart disease, number of heart valve surgery, complications, etc. was collated.

Mishel uncertainty in illness scale: Mishel uncertainty in illness scale (MUIS) developed by Mishel was used to investigate and analyze illness uncertainty in patients one day before operation and one day before hospital discharge, to better formulate and implement intervention strategies, and ultimately reduce the level of stress felt by patients and promote their rehabilitation [8]. This scale consisted of 33 items representing four dimensions: ambiguity, complexity, lack of information and unpredictability. Each item was answered on a 5-point Likert scale with responses ranging from strongly agree (5 points) to strongly disagree (1 point). The total score was between 32 to 160 points, which was divided into three grades: low level (32-74.7 points), medium level (74.8-117.4 points), and high level (117.5-150 points).

Social support rating scale: The social support rating scale was used to evaluate the level of social support for patients one day before operation, and to understand the characteristics of patients' social support and its relationship with patients' mental health, mental disorder and various physical diseases [9]. The scale comprised 10 items representing three dimensions: objective support, subjective support and utilization of social support. A single composite score was produced.

Self-efficacy scale: Self-efficacy scale developed for the chronic disease self-management study was used to understand patients' attitudes toward their own behavior, and their expectations and predictions of their own behavior as well as effects of their behavior [10]. The scale included two dimensions: self-efficacy to manage diseases in general and self-efficacy to manage symptoms. The self-efficacy scores were divided into three grades: high level (≥7 points), medium level (≥5 points and <7 points) and low level (<5 points).

Medical coping modes questionnaire: Medical coping modes questionnaire (MCMQ) was used to investigate and analyze the psychological states and coping modes of patients one day before operation and one day before hospital

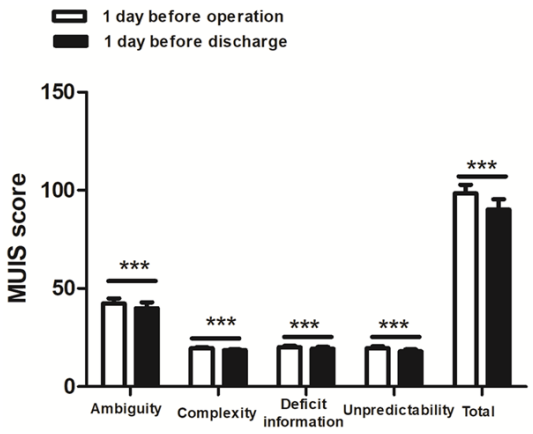

Figure 1. MUIS scores for patients before and after heart valve surgery. Note: ***P<0.001. MUIS, Mishel Uncertainty in Illness Scale.

discharge [11]. The scale consisted of 20 items representing three dimensions: confrontation, avoidance and resignation.

Connor-Davidson resilience scale: Connor-Davidson resilience scale (CD-RISC) was used to quantify patients' mental ability to adapt to adversity one day before operation and one day before hospital discharge. The scale included three dimensions: self-reliance, optimism and resilience, with the total score ranging from 0 to 100 points [12].

Survey methods

A face-to-face survey of the patients was conducted by researchers who had received professional training. Before the questionnaire was handed out, the purpose and content of the survey were explained to the patients. After giving their informed consent, the patients completed the questionnaires anonymously, and the researchers used uniform instructions to give consistent answers to patients' inquires. Questionnaires were collected on the spot. The researchers checked whether or not there were unanswered questions. If there were any missing responses, patients were promptly asked to give their answers.

Statistical methods

The SPSS 22.0 statistical software was used to analyze the data. T-test was used to compare the measurement data. χ^2 test was used to compare the enumeration data. Pearson correlation was used to analyze the correlation between various factors and illness uncertainty in patients. Score for uncertainty was the dependent variable, and gender, age, years of education, monthly family income, marital status, medical insurance, number of heart valve surgeries, surgical method, complication and level of self-efficacy were independent variables. Univariate analysis was performed to analyze both kinds of variables. Multivariate logistic regression analysis was then performed to analyze statistically significant variables to further explore the relevant factors that had an impact on patients' feelings of uncertainty in illness. P<0.05 meant the difference was statistically significant, and P<0.001 meant the difference was highly significant.

Results

Changes in MUIS scores for patients before and after heart valve surgery

The scores of ambiguity, complexity, lack of information, and unpredictability and the total MUIS scores for patients one day before discharge were significantly lower than those for patients one day before operation (P<0.001, **Figure 1**).

Univariate analysis of factors influencing patients' total MUSI scores before operation

Univariate analysis was performed to analyze factors that possibly had an impact on patients' total MUSI scores before operation. The results showed that patients' age, years of education, average monthly family income, marital status, number of heart valve surgeries, complications and self-efficacy significantly affected patients' feelings of uncertainty in illness before operation (P<0.05, **Table 1**).

Changes in scores for each dimension of CD-RISC and total CD-RISC scores before and after operation

The scores of resilience, self-reliance, optimism and total scores for patients one day before discharge were significantly higher than those for patients one day before operation (P<0.01, **Figure 2**).

Changes in coping modes of patients before and after operation

The confrontation score for patients one day before discharge was significantly higher than that for patients one day before operation

Table 1. Univariate analysis of factors influencing patients' total MUSI scores before operation

Factors	Number of patients	MUSI score	t/F	P
Gender			1.941	0.054
Male	92	95.72±10.21		
Female	70	98.75±9.33		
Age (years old)			3.998	0.020
≤39	35	80.32±11.83		
40~60	69	93.28±8.99		
>60	58	117.36±9.75		
Years of education (years)			7.187	<0.001
≤9	76	99.83±7.38		
>9	86	91.74±6.94		
Average family monthly income (RMB)			21.040	<0.001
<1500	38	102.64±7.85		
1500-3000	64	97.66±8.94		
>3000	60	92.03±7.03		
Marital status			30.890	<0.001
Unmarried	79	90.21±6.38		
Married	63	98.32±8.10		
Divorced/Widowed	20	101.73±8.95		
Medical Insurance			1.751	0.082
Yes	112	95.39±9.37		
No	50	98.26±10.21		
Number of heart valve surgeries			4.885	<0.001
Once	136	93.27±12.42		
Twice	26	106.18±11.95		
Surgical methods			1.206	0.302
Heart valve replacement	31	95.38±9.27		
Heart valvuloplasty	38	96.31±10.22		
Valve replacement-valvuloplasty combination	93	98.11±8.95		
Complications*			6.930	<0.001
Yes	53	104.27±13.25		
No	109	92.75±7.84		
Self-efficacy			29.610	<0.001
Low	45	103.47±7.31		
Medium	64	99.73±6.44		
High	53	92.31±8.46		

Note: *Complications include chronic diseases such as hypertension, hyperlipidemia, and diabetes.

(P<0.001), while the avoidance and resignation scores were significantly lower than those for patients one day before operation (P<0.05, **Figure 3**).

Pearson correlation analysis

Pearson correlation analysis showed that there was a negative correlation between the total MUSI scores one day before operation and resilience, self-reliance, optimism, confrontation, resignation, utilization of support, objective support and total social support (P<0.05). There was a significant positive correlation between the total MUSI scores and avoidance (P<0.05, **Table 2**).

Multivariate logistic regression analysis

Multivariate logistic regression analysis showed that age, years of education, number of heart valve surgeries, monthly family income,

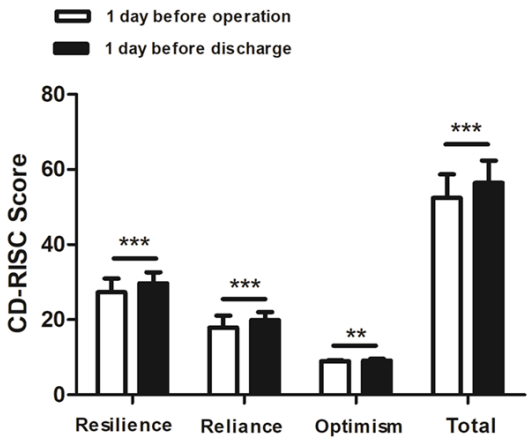

Figure 2. Changes in scores for each dimension of CD-RISC and total CD-RISC scores before and after operation. Note: **P<0.01, ***P<0.001. CD-RISC, Connor-Davidson resilience scale.

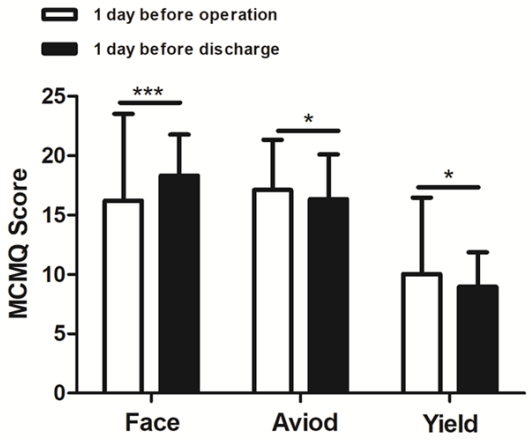

Figure 3. Changes in coping modes of patients before and after operation. Note: *P<0.05, ***P<0.001. MCMQ, medical coping modes questionnaire.

self-reliance, optimism, confrontation and resignation entered into the regression model were important risk factors influencing illness uncertainty in patients before operation (P< 0.05, **Table 3**).

Discussion

At present, heart valve surgery is one of the main treatments for severe thickening, malformation and limited movement of heart valves [13]. This study explored and analyzed the illness uncertainty in patients undergoing heart valve surgeries and the related factors. The correlation between patients' general information, psychological resilience, coping modes, social support, self-efficacy and illness uncertainty was analyzed. The results of this study showed that most patients undergoing heart valve surgeries were at a medium level of uncertainty, which was consistent with the results of most studies done in China and abroad [14, 15]. For example, Li et al. investigated 208 cardiac valvular surgery patients with cardiopulmonary bypass one day before operation and one day before discharge in the department of cardiovascular surgery in four upper first-class (also known as Grade 3, Class A) hospitals in Guangdong Province. The results showed that the average total MISU scores for patients were 99.09±11.41 points, with 92.3% of patients having a medium level of uncertainty [15]. The patients' feelings of uncertainty in illness mainly resulted from the unpredictability of the treatment and prognosis of the disease. The difficulty and high risk of the surgery, the high incidence of postoperative complications, and the unpredictable nature of prognosis all contribute to illness uncertainty in patients. In addition, as patients need to take anticoagulants for the rest of their life and need regular medical check-ups after the operation, they are prone to feel uncertain about the procedures of follow-up visits and matters needing attention after hospital discharge [16]. This study showed that the level of illness uncertainty in patients one day before hospital discharge was significantly lower than that one day before operation. It demonstrated that the patients' feelings of uncertainty in illness were less intense after a series of medical treatments and education intended to raise patients' awareness of the disease, which served as proof of the value of awareness-raising education in easing patients' feelings of uncertainty in illness. Therefore, efforts to educate patients about disease prevention, surgical treatments and post-operative rehabilitation before operation should be stepped up, so as to further reduce the level of preoperative illness uncertainty in patients.

In this study, univariate and multivariate logistic regression analysis was performed. Variables including patients' age, years of education, the number of heart valve surgeries, monthly family income, self-reliance, optimism, confrontation and resignation entered into the regression model and were important risk factors affecting patients' feelings of uncertainty

Table 2. Pearson correlation analysis of the correlation between patients' total MUSI scores one day before operation and patients' mental resilience, coping modes and social support level

	Resilience	Self-reliance	Optimism	Confrontation	Avoidance	Resignation	Utilization of support	Objective support	Total social support	Total MUSIscore
Resilience	1									
Self-reliance	0.694**	1								
Optimism	0.517**	0.482**	1							
Confrontation	0.498**	0.306**	0.289**	1						
Avoidance	-0.213*	0.082	0.073	-0.089	1					
Resignation	-0.627**	-0.397**	-0.285**	-0.231*	0.176*	1				
Utilization of support	0.206*	0.316**	0.225*	0.278*	-0.047	-0.077	1			
Objective support	0.116	0.297**	0.121	0.198*	-0.215*	-0.164*	0.362**	1		
Total social support	0.247*	0.352**	0.343**	0.214*	-0.195*	-0.095	0.446**	0.317**	1	
Total MUSI score	-0.602**	-0.482**	-0.206*	-0.531**	0.214*	-0.574**	-0.314**	-0.278**	-0.394**	1

Note: *P<0.05; **P<0.01.

Table 3. Multivariate logistic regression analysis of relevant factors influencing patients' total MISU scores one day before operation

Important factors	Regression system	Standard error	Standard regression coefficient	P	OR	95% CI
Age	1.416	0.612	0.168	0.011	2.647	1.763~4.273
Years of education	-1.748	0.527	-0.183	0.025	2.175	1.364~3.392
Number of heart valve surgeries	0.978	0.468	0.127	0.031	1.795	1.285~3.116
Family monthly income	-0.201	0.718	-0.159	0.005	3.182	2.647~5.842
Self-reliance	-0.687	0.178	-0.315	0.000	3.784	3.145~6.027
Optimism	-1.087	0.352	-0.213	0.006	2.978	2.316~5.882
Confrontation	-0.974	0.185	-0.286	0.002	2.674	1.977~4.038
Resignation	1.264	0.275	0.351	0.000	3.641	2.950~7.312

Note: OR, odds ratios; CI, confidence interval.

before operation. With age, patients were likely to experience a higher level of uncertainty in illness. The main reasons were that elderly patients had a higher risk of concurrent underlying diseases, and degenerative changes in organ function as well as reduced immune function of the body [17]. In addition, patients with fewer years of education and lower monthly family income had higher levels of uncertainty in illness. As patients with fewer years of education had lower education level, they usually had poorer knowledge of the treatment and prognosis of the disease, resulting in their higher level of uncertainty in illness. For patients with lower income, because the cost of surgeries could be a huge financial burden on their families, and they needed to take medications for the rest of their life after operation, they would also feel higher level of uncertainty about the disease. These results were consistent with the results of studies done by other scholars [18]. For patients who underwent another heart valve surgery, they felt a heightened level of illness uncertainty, because of the long course of the disease, the presence of different degrees of cardiac function damage and concurrent organ dysfunction, highly difficult surgical procedures, high mortality rate and high incidence of postoperative complications. Therefore, it was suggested that attempts should be made to offer customized health education to patients based on their individual characteristics in clinical work, so as to relieve patients' feelings of uncertainty before operation and promote postoperative recovery [19].

Psychological resilience refers to an individual's ability to adapt to trauma, threat, adversity or other major stressful events in life; its three aspects are resilience, self-reliance and optimism [20]. The results of correlation analysis showed that psychological resilience was a negative factor affecting the level of uncertainty felt by patients undergoing heart valve surgeries. Patients with poor psychological resilience had weak confidence in the treatment of diseases because of their own coping ability and psychological quality. They might succumb to the thought that they could not do anything about the disease, and adopted the coping modes of avoidance and resignation, which led to the lack of information during the process of surgical treatment and post-operative rehabilitation [21]. Therefore, in clinical treatment, for patients with poor psychological resilience, medical staff should find ways to further enhance patients' confidence in disease treatment and reduce their uncertainty in illness by improving their psychological resilience. Coping is an individual's cognitive, constant and behavioral effort to manage specific external and/or internal demands as well as external shocks. It is a mean to alleviate stress and includes the individual's assessment of stress events and regulation of relevant emotional responses to them [22]. Positive coping style is characterized by being positive, active and enterprising, while negative coping style is characterized by being passive, negative and restrained. Confrontation, as a positive coping style, can effectively reduce the pressure felt by patients and enhance their confidence to defeat the disease. Positive coping enables patients to seek effective ways to solve problems in the long course of a disease, thus helping patients to reduce their uncertainty in illness [23]. Avoidance and resignation, as ne-

gative coping styles, can temporarily relieve the pressure felt by patients, but they are not conducive to the long-term physical and mental health of patients, and may hinder patients' efforts to makes sense of the information related to disease treatment and prognosis, thus increasing illness uncertainty in patients. Therefore, in the course of clinical treatment, medical staff should help patients to adopt a positive coping style, prevent patients from feeling uncertain about the disease treatment and prognosis, and cater for patients' needs for disease-related knowledge, so as to reduce patients' uncertainty in illness.

In conclusion, the uncertainty felt by patients undergoing heart valve surgeries is at a medium level. Age, education level, number of heart valve surgeries, monthly family income, psychological resilience and coping modes are the main factors affecting illness uncertainty in patients. Therefore, in the course of clinical treatment, more efforts should be made to educate patients about the disease based on their individual characteristics, and help them improve their psychological resilience as well as adopt positive coping styles, so as to alleviate their uncertainty in illness.

However, this study was a single-center study, and the sample size was small. A multi-center and large-sample study is needed to verify the conclusion of this study in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Lihua Zhou, College of Nursing, Anhui Medical University, No. 15 Feicui Road, Economic and Technological Development District, Hefei 230000, Anhui Province, China. Tel: +86-0551-63869169; Fax: +86-0551-63869169; E-mail: zhoulihua85dc@163.com

References

[1] Renda G, Ricci F, Giugliano RP and De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Am Coll Cardiol 2017; 69: 1363-1371.

[2] Okamura H, Kimura N, Tanno K, Mieno M, Matsumoto H, Yamaguchi A and Adachi H. The impact of preoperative sarcopenia, defined based on psoas muscle area, on long-term outcomes of heart valve surgery. J Thorac Cardiovasc Surg 2018; [Epub ahead of print].

[3] Giammanco MD, Polimeni G, Spadaro L, Gitto L, Buccafusca M and Bramanti P. An initial validation of the italian mishel uncertainty illness scale (MUIS) for relapsing remitting multiple sclerosis patients. Neurol Sci 2014; 35: 1447-1452.

[4] Chang CM and Yeh HD. Uncertainty estimation in one-dimensional heat transport model for heterogeneous porous medium. Ground Water 2014; 52: 326-331.

[5] Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, Ortega BN, Zaiko YV, Roach EL, Korgaonkar MS, Grieve SM, Galatzer-Levy I, Fox PT and Etkin A. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 2015; 72: 305-315.

[6] Kazer MW, Bailey DE Jr, Chipman J, Psutka SP, Hardy J, Hembroff L, Regan M, Dunn RL, Crociani C, Sanda MG; PROSTQA Consortium Study Group. Uncertainty and perception of danger among patients undergoing treatment for prostate cancer. BJU Int 2013; 111: E84-91.

[7] Moon H, Kim SB, Chen JJ, George NI and Kodell RL. Model uncertainty and model averaging in the estimation of infectious doses for microbial pathogens. Risk Anal 2013; 33: 220-231.

[8] Schlosser RJ, Gage SE, Kohli P and Soler ZM. Burden of illness: a systematic review of depression in chronic rhinosinusitis. Am J Rhinol Allergy 2016; 30: 250-256.

[9] Liu SM. Effects of social support on health self-management skill and depression of elderly patients with cardiovascular disease. Chinese Journal of Modern Nursing 2017; 23: 188-193.

[10] Chen B and Chen L. Reliability and validity of Chinese version Self-efficacy for Appropriate Medication Use Scale in the coronary heart disease patients. Chinese Journal of Modern Nursing 2017; 23: 1837-1842.

[11] Rong X, Peng Y, Yu H and Li D. Factors associated with adoption of coping strategies among Chinese patients with heart failure in ethnic minority regions. J Clin Nurs 2018; 27: 3324-3334.

[12] Adami HO, Bretthauer M, Emilsson L, Hernan MA, Kalager M, Ludvigsson JF and Ekbom A. The continuing uncertainty about cancer risk in inflammatory bowel disease. Gut 2016; 65: 889-893.

[13] Tosoian JJ and Carter HB. Active surveillance of localized prostate cancer: acknowledging uncertainty. J Clin Oncol 2016; 34: 4452.

[14] Bijman RG, Breedveld S, Arts T, Astreinidou E, de Jong MA, Granton PV, Petit SF and Hooge-

man MS. Impact of model and dose uncertainty on model-based selection of oropharyngeal cancer patients for proton therapy. Acta Oncol 2017; 56: 1444-1450.

[15] Li YJ, Xie WH, Li M, Yu Y, Lin KX, Pan YY and Zhuang SH. The current status and influential factors of uncertainty in illness in cardiac valvular surgery patients with cardiopulmonary bypass. Chinese Journal of Behavioral Medicine and Brain Science 2014; 23: 148-151.

[16] Tan HJ, Marks LS, Hoyt MA, Kwan L, Filson CP, Macairan M, Lieu P, Litwin MS and Stanton AL. The relationship between intolerance of uncertainty and anxiety in men on active surveillance for prostate cancer. J Urol 2016; 195: 1724-1730.

[17] Etkind SN and Koffman J. Approaches to managing uncertainty in people with life-limiting conditions: role of communication and palliative care. Postgrad Med J 2016; 92: 412-417.

[18] Verbeke C, Lohr M, Karlsson JS and Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev 2015; 41: 17-26.

[19] Crispen PL. Small renal masses: the effect of illness uncertainty during active surveillance. Nat Rev Urol 2013; 10: 255-256.

[20] Oishi A and Murtagh FE. The challenges of uncertainty and interprofessional collaboration in palliative care for non-cancer patients in the community: a systematic review of views from patients, carers and health-care professionals. Palliat Med 2014; 28: 1081-1098.

[21] Gravis G, Audenet F, Irani J, Timsit MO, Barthelemy P, Beuzeboc P, Flechon A, Linassier C, Oudard S, Rebillard X, Richaud P, Roupret M, Thiery Vuillemin A, Vincendeau S, Albiges L and Rozet F. Chemotherapy in hormone-sensitive metastatic prostate cancer: evidences and uncertainties from the literature. Cancer Treat Rev 2017; 55: 211-217.

[22] Lin L, Chien LC, Acquaye AA, Vera-Bolanos E, Gilbert MR and Armstrong TS. Significant predictors of patients' uncertainty in primary brain tumors. J Neurooncol 2015; 122: 507-515.

[23] Nguyen J, Moteabbed M and Paganetti H. Assessment of uncertainties in radiation-induced cancer risk predictions at clinically relevant doses. Med Phys 2015; 42: 81-89.