Research Report

Quality of Life and Anxiety in Patients with First Diagnosed Non-Muscle Invasive Bladder Cancer Who Receive Adjuvant Bladder Therapy

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Abstract.
BACKGROUND: Bladder cancer (BC) is one of the most common malignancies (4.5% of all newly diagnosed cases worldwide). Most of the new BC cases are diagnosed as non-muscle invasive BC (NMIBC), needing continuous follow up after primary endoscopic therapy. Adjuvant bladder therapy with chemo- or immuno- agents, apart from the initial diagnosis, the strict surveillance program and the risk of recurrence, may have a major impact on the patients' physical and mental health.
OBJECTIVE: We evaluated anxiety and quality of life (QoL) in patients who underwent surgery for NMIBC and followed a bladder instillation programme.
METHODS: This is a prospective analysis of patients with histopathologically confirmed NMIBCs. Eligible were all adult patients with a single or multiple NMIBCs who underwent a transurethral tumor resection and followed a therapy with either BCG or Epirubicin instillations. The SF-36 questionnaire Physical and Mental health aspects were used for QoL assessment. Similarly, the STAI-Y was introduced for the state (STAI-Y1) and trait anxiety (STAI-Y2) evaluation.
RESULTS: 117 eligible patients were screened, with 108 entering finally the study; 9 patients were excluded due to disease recurrence. 17 patients (15.7%) received Epirubicin (Ta-T1, Low Grade tumors), whereas 91 patients (84.3%) received BCG (T1, High Grade). Regarding SF-36 Physical a 6 months decrease was followed by an improvement at 12 months ($p = 0.008$). Similarly, an increase of the SF-36 Mental health score was identified ($p = 0.03$). In contrast to STAI-Y2 scores ($p = 0.945$), a

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long-term reduction of the state anxiety was identified ($p = 0.001$). Preoperative SF-36 Physical was inversely correlated with age ($p = 0.029$), while absence of alcohol was associated with lower mental health ($p = 0.003$). Overall, patient characteristics, habits and the administered treatment did not affect the postoperative QoL and anxiety.

CONCLUSION: Patient QoL and anxiety improved during follow up. Still, further larger scale studies are required to support our findings.

INTRODUCTION

Bladder cancer (BC) is one of the most common malignancies, accounting for almost 4.5% of all newly diagnosed cases worldwide [1]. The annual incidence of BC is 180,000 new cases, whereas the mortality rate is estimated to be more than 55,000 patients per year. The gradually ageing population and the increased exposure to several risk factors are expected to further increment the burden of BC [2].

Most new BC cases are diagnosed as non-muscle invasive BC (NMIBC) [3]. Current approach for the NMIBC management is based on the transurethral resection of the tumor followed by a strict follow-up schedule that may include intravesical administration of chemotherapeutic or immune-modifying regimens. Even though 5-year overall survival of NMIBC is 96% [4], recurrence is quite common, with the 1st and the 5th year rate being 33% and 50%, respectively. As a result, patients are required to undergo successive cystoscopies and adjuvant treatments [5].

Initial diagnosis, the strict surveillance program and the risk of recurrence have a major impact on the patients' physical and mental health [6–8]. Furthermore, NMIBC intravesical treatment several adverse events, affecting patients' quality of life (QoL). The most common complaint of patients receiving bladder instillations for NMIBC is lower urinary tract symptoms (LUTS) [9]. Indeed, several studies attempted to evaluate factors of the detrimental effect of the NMIBC therapeutic approaches on the psychological and physical health, with methodological issues [3, 6, 7, 10]. The application of generic and widely validated tools, such as SF-36 and STAI-Y, allows for the overall assessment of the QoL and anxiety, respectively [11]. However, current evidence regarding the perioperative QoL and anxiety patterns of NMIBC patients on the basis of SF-36 and STAI-Y are minimal [12].

In this study we tried to evaluate the QoL and the anxiety response in patients suffering from NMIBC who underwent surgery and they had adjuvant intravesical therapy with bladder instillations.

METHODS

Inclusion criteria

The present study is a prospective analysis of all patients who underwent surgery for NMIBC in our tertiary center, between 2018– 2020 and were planned to receive adjuvant intravesical therapy (Fig. 1). As such, all adult patients (age: 18–80 years) with histopathologically confirmed NMIBC (pTis, pTa, pT1) entered our study. An institutional ethics approval was received (Approval number: 4212/27-07-2018). All eligible patients provided a written informed consent. The study adhered to the Helsinki Declaration [13] and was reported on the basis of the STROBE guidelines [14].

Exclusion criteria

Patients with severe comorbidities (ASA > III), muscular invasive bladder cancer, previous malignancy, recurrent bladder cancer, refusal to participate, and patients that were, either, not fluent Greek speakers, or who did not adhere to the follow up schedule were excluded.

Study protocol

All patients underwent endoscopic resection of the bladder tumor under spinal anesthesia. Three weeks postoperatively they initiated adjuvant intravesical therapy of either BCG or Epirubicin instillations on an outpatient basis, as described elsewhere [15].

Demographics (age, gender, educational level, marital status, residence and employment status) and habitual data (smoking, alcohol) were recorded for all eligible patients. The SF-36 questionnaire was introduced for the QoL assessment. This tool has been previously validated in the Greek population [16] and its efficacy in the overall QoL evaluation has been extensively confirmed in various settings [17]. All eight subscales of the questionnaire are sub-grouped in two major components, the Physical
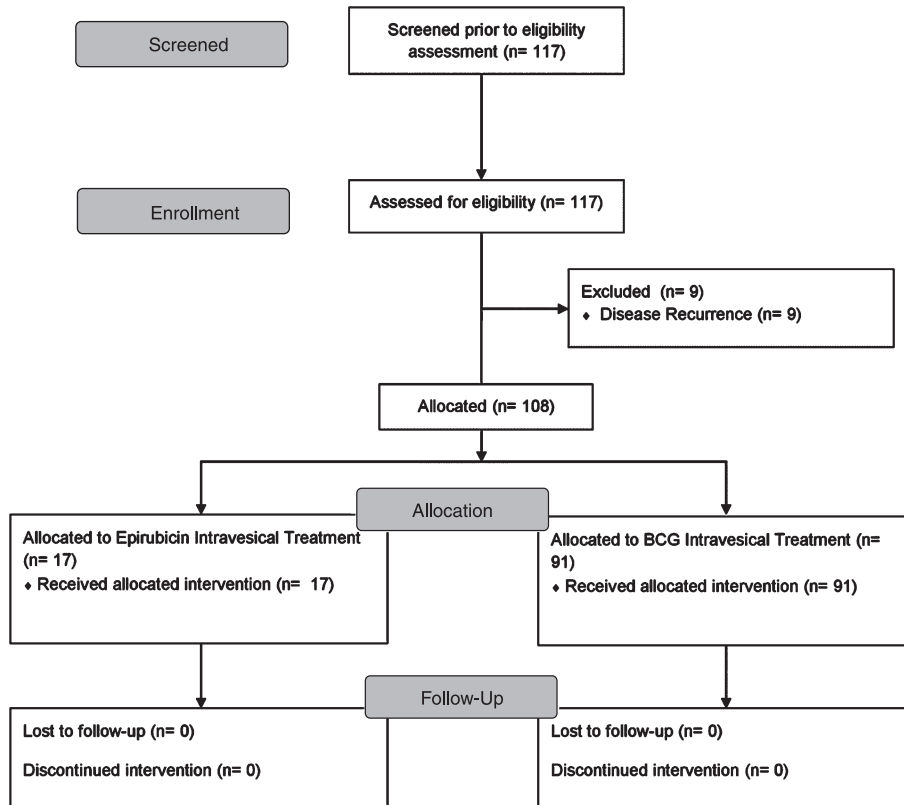
Fig. 1. Study flow-chart.

(Physical Functioning -PF, Role Physical-RP, Bodily Pain-BP and General Health-GH) and Mental (Vitality-VT, Mental Health-MH, Role Emotional-RE and Social Functioning-SF) health aspect. State anxiety echoes the psychological and physiological temporary way of reacting in a specific moment. On the other hand, the trait anxiety refers to a more stable pattern of behavior, reflecting someone's personality. Results range from 0 to 100, with the latter being the optimal outcome. Consistently, anxiety levels were estimated by the validated State-Trait Anxiety Inventory (STAI-Y) questionnaire [18]. The two subscales of this tool address the state (STAI-Y1) and trait anxiety (STAI-Y2) of the subject. Scores ranging from 29–39 were considered as low, whereas values greater that 60 were translated as increased anxiety. Patient evaluation was performed 2 weeks preoperatively and during the scheduled postoperative follow up (3, 6 and 12 months after surgery) examination. All data was secured in an encrypted electronic repository.

The primary endpoint of our study was the assessment of the SF-36 Physical health aspect variations during the follow up period. Secondary endpoints

were the evaluation of the time fluctuations of SF-36 Mental, STAI-Y1 and STAI-Y2. Moreover, an association analysis of patient characteristics with the preoperative and postoperative QoL and anxiety measurements was performed. Based on the reliability of the questionnaires, the minimum required number of sampling observations (power: 80%, effect size: 0.3, type I error: 5%) was estimated at the level of 90 cases.

All data underwent a Shapiro-Wilk test for normality. Independent samples t test was used for continuous variables. Given an incompetence to confirm normality, the evaluation of a possible relationship between distinct patient characteristics and the preoperative QoL and anxiety levels was based on the Mann-Whitney U and the Kruskal-Wallis H test. In order to examine the time-related variations of the questionnaire measurements, a repeated measures ANOVA model (RM-ANOVA) was introduced. Violation of the sphericity assumption was assessed by the Mauchly's test of sphericity. If a violation was confirmed, then a Greenhouse-Geisser correction was applied. Post hoc comparisons and interactions of

time endpoints and patient characteristics were calculated. The effect of distinct characteristics on the measured variables was estimated by the F test. Cronbach's Alpha was, also, calculated for the evaluation of the internal consistency of the questionnaires in each time endpoint.

Categorical variables were provided as N (Percentage), whereas continuous data were reported as Mean (Standard Deviation). For all analyses, mean $\pm 2SE$ was displayed through all time endpoints. Statistical significance was considered at the level of $p < 0.05$. All analyses were completed in SPSS version 23 software (SPSS Inc. Chicago, IL, USA).

RESULTS

117 eligible patients were initially screened, with 108 entering finally the study (97 males and 11 females); 9 patients were excluded due to disease recurrence. Patients' characteristics and habits are shown on Table 1. Most cases were never exposed to alcohol (35.2%), in contrast to smoking (11.1%). According to pathology, 17 patients (15.7%) received epirubicin (Ta-T1, Low Grade tumors), whereas 91 patients (84.3%) received BCG (T1, High Grade). Overall, 75% of patients had no therapy-related adverse event (Table 1 and Supplementary Material Tables), while dysuria and hematuria were reported in 19% and 8% respectively. All patients tolerated therapy well; there were no withdrawals due to therapy symptoms or technical issues (i.e, catheterization, instillation, etc).

The fluctuation of the SF-36 Physical over the progressive time endpoints is visualized in Fig. 2. Mean values at 3 months were comparable to the preoperative measurements. The 6 months decrease was followed by a significant improvement at 12 months. Overall, RM-ANOVA (Table 2) confirmed the presence of a significant time variation ($p = 0.008$).

Similarly, a significant ($p = 0.03$) increase of the SF-36 Mental health score (Fig. 3) was identified. As shown in Table 2, a higher 12-month mean value was estimated (72.2), compared to the respective preoperative assessment (64.2). In terms of anxiety, analysis confirmed a long-term decrease (Fig. 4) of the state anxiety (preoperative STAI-Y1:41.2, 12 months STAI-Y2:33, $p = 0.001$). In contrast to these, STAI-Y2 reports (Fig. 5) were consistent over the time endpoints ($p = 0.945$).

Preoperative SF-36 Physical scores were inversely ($p = 0.029$) correlated with age (Table 1 and Supplementary Material Figures). Absence of alcohol

Table 1
Patients' demographics

|		N	Percentage (%)
Gender	Male	97	89.8
	Female	11	10.2
Age	<66 years	40	37.0
	66 + years	68	63.0
Tumor Stage	Ta-T1, Low Grade	17	15.7
	T1, High Grade	91	84.3
Educational Level	No Primary Education	3	2.8
	Primary Education	49	45.4
	Secondary Education	26	24.1
	Higher Education	26	24.1
	MSc	4	3.7
	PhD	0	0.0
Marital Status	Unmarried	2	1.9
	Married	92	85.2
	Divorced	8	7.4
	Widowed	4	3.7
	Cohabitation	2	1.9
Residence	Local Prefecture	75	69.4
	Local Region	27	25.0
	Outside Local Region	6	5.6
Employment Status	Employed	20	18.5
	Retired	83	76.9
	Unemployed	4	3.7
	Household	1	0.9
Smoking	No	12	11.1
	Ex-smoker	60	55.6
	Yes	36	33.3
Alcohol	No	38	35.2
	Social consumption	56	51.9
	Daily	14	13.0
Treatment	BCG	91	84.3
	Epirubicin	17	15.7
Adverse Events	None	81	75
	Dysuria	19	19
	Microscopic Hematuria	8	8
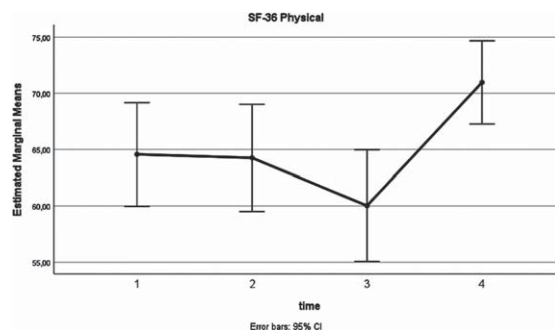
Fig. 2. SF-36 Physical (x-axis: 1: preoperatively, 2: at 3 months postoperatively, 3: at 6 months postoperatively, 4: at 12 months postoperatively).

Table 2
Basic questionnaire results

Subscale	Time	Mean	Standard Deviation	Mauchly's Sphericity *P*	Time Variation *P*
SF-36 Physical	2 weeks preoperatively	64.6	24.1	**0.011**	**0.008**[*]
	3 months postoperatively	64.3	24.9		
	6 months postoperatively	60.0	25.9		
	12 months postoperatively	71.0	19.4		
SF-36 Mental	2 weeks preoperatively	64.2	24.4	**0.011**	**0.03**[*]
	3 months postoperatively	61.1	26.2		
	6 months postoperatively	64.1	22.7		
	12 months postoperatively	72.2	18.3		
STAI-Y1	2 weeks preoperatively	41.2	11.1	**0.023**	**0.001**[*]
	3 months postoperatively	42.1	14.7		
	6 months postoperatively	40.7	13.6		
	12 months postoperatively	33.0	9.3		
STAI-Y2	2 weeks preoperatively	44.0	9.3	0.362	0.945
	3 months postoperatively	44.0	11.3		
	6 months postoperatively	44.6	12.1		
	12 months postoperatively	43.8	11.8		

[*]Greenhouse-Geisser correction applied STAI score: 29–39: low anxiety 40–59: moderate anxiety 60–80: high anxiety SF-36 score: 0: minimum value 100: maximum value.
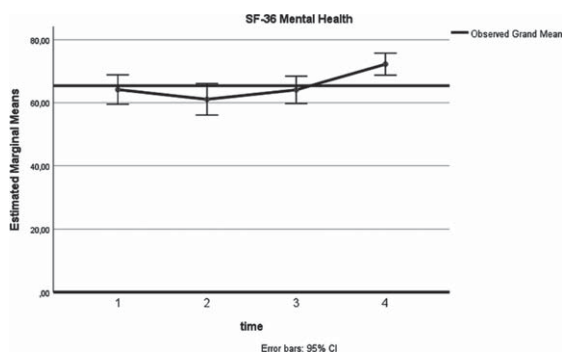

Fig. 3. SF-36 Mental (x-axis: 1: preoperatively, 2: at 3 months postoperatively, 3: at 6 months postoperatively, 4: at 12 months postoperatively).
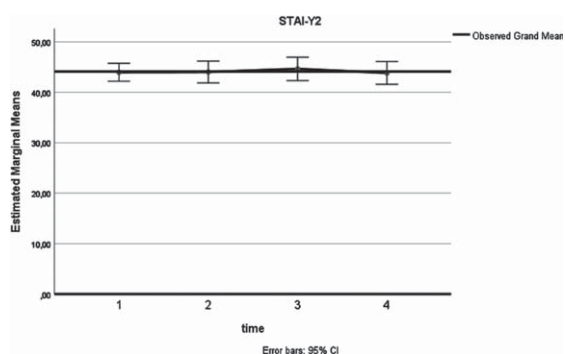

Fig. 5. STAI-Y (x-axis: 1: preoperatively, 2: at 3 months postoperatively, 3: at 6 months postoperatively, 4: at 12 months postoperatively).
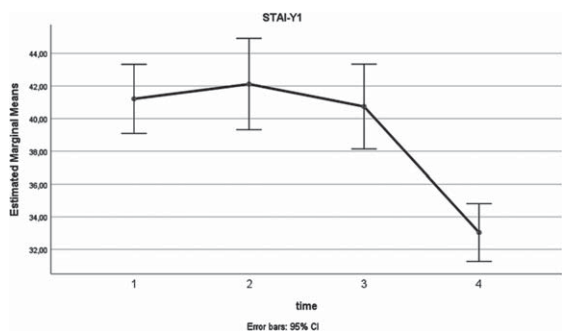

Fig. 4. STAI-Y1 (x-axis: 1: preoperatively, 2: at 3 months postoperatively, 3: at 6 months postoperatively, 4: at 12 months postoperatively).

consumption was associated with significantly lower values in mental health (SF-36 Mental $p = 0.003$). Gender, educational level and smoking did not affect the preoperative QoL and anxiety levels, while tumor stage and residence status correlated with the preoperative STAI-Y1 scores (Table 3 and Supplementary Material Figures).

A significant interaction of age ($p = 0.011$) and alcohol consumption ($p = 0.015$) with time in the Physical aspect of the SF-36 was documented (Supplementary Material Figures). However, there was no significant effect ($p = 0.605$ and $p = 0.89$) of these variables on the mean tool measurements. Moreover, a significantly different pattern of SF-36 Mental ($p = 0.02$), STAI-Y1 ($p = 0.011$) and STAI-Y2 ($p = 0.003$) scores, over the successive time endpoints was identified in the various alcohol consumption subgroups. A significant effect of alcohol was not confirmed in any tool. Overall, patient characteristics, habits, the administered treatment and the adverse

Table 3
The effect of patient characteristics on quality of life and anxiety measurements

Subscale	Factor	P
SF-36 Physical	Gender	0.499
	Age	**0.029**
	Tumor Stage	0.478
	Educational Level	0.188
	Marital Status	0.475
	Residence	0.123
	Smoking	0.862
	Alcohol	0.325
SF-36 Mental	Gender	0.733
	Age	0.483
	Tumor Stage	0.109
	Educational Level	0.386
	Marital Status	0.413
	Residence	0.878
	Smoking	0.424
	Alcohol	**0.003**
STAI-Y1	Gender	0.764
	Age	0.597
	Tumor Stage	**0.04**
	Educational Level	0.299
	Marital Status	0.361
	Residence	**0.040**
	Smoking	0.313
	Alcohol	0.109
STAI-Y2	Gender	0.452
	Age	0.386
	Tumor Stage	0.46
	Educational Level	0.495
	Marital Status	0.170
	Residence	0.213
	Smoking	0.575
	Alcohol	0.102

events did not affect the postoperative QoL and anxiety (Supplementary Material Figures).

Based on the sample size, the power of the present study was estimated at the level of 87.1%. *Post-hoc* analysis of the questionnaires' internal consistency revealed an adequate level of validity (Cronbach Alpha: 72.4%–93.7%) (Table 4). Exceptions were the 6-months SF-36 Mental and the 12-months STAI-Y1 measurements (6% and 35% respectively).

DISCUSSION

Summary of evidence

QoL corresponds to the gratification level of an individual's physical, mental, and social needs and therefore is accomplished through the interaction of various components. The inherent difficulty in differentiating between the subjective and objective components renders QoL assessment a challenging task [19]. Taking into consideration the variability of the available techniques, valid QoL evaluation is based on the suitability of the applied methods. Although the design of most of these tools address samples with heterogeneous base characteristics, the QoL assessment in specific patient categories require the introduction of specified questionnaires. Overall, QoL assessment tools are assigned in two subgroups. General indicators study generic aspects of physical and psycho-social functionality, whether specific assessment tools emphasize on the individual's perception regarding health and HRQoL [20].

NMIBC has a significant impact on a patient's QoL. The initial cancer diagnosis, the frequent cystoscopies and the adverse events related to the intravesical therapy affect the physical function, the mental health, the reported fatigue and the role function [6]. The detrimental effect of a BC diagnosis on QoL was reported by Singer et al. [21]. Even though no differences between non-muscle invasive and muscle-invasive bladder cancer patients were found, both groups had decreased physical and emotional functioning compared to the general population. Interestingly, QoL increased with time in all patient groups ($p < 0.001$).

Similarly, Fung et al. confirmed a significant post-diagnosis reduction of the physical and mental scores between the prediagnosis and post-diagnosis groups (–2.7, 95% CI –3.8, –1.7 vs –1.4, 95% CI –2.6, –0.3). In patients with non-muscle invasive bladder cancer the physical and mental score differences were –1.9 ($p < 0.01$) and –1.4 ($p = 0.01$), respectively. In those with muscle invasive bladder cancer there was a statistically and clinically significant difference in the physical but not the mental score (–5.3, $p < 0.01$ vs –2.7, $p = 0.07$). The effect on the physical domain had a duration of 10 years [22].

In a prospective analysis by Schmidt et al., it was estimated that the impact of NMIBC on mental health was detectable during the 6-month follow-up period [23]. Mental health was significantly worse than SF-36 scores at diagnosis (mean of 49.7 vs. 53.3, 95% CI: 52.5–54.2). Urinary domain improved significantly from diagnosis (85.2, 95% CI: 82.9–87.4) to 12-month evaluation (90.2, 95% CI: 87.7–92.8), whereas sexual domain decreased from 56.4 (95% CI: 52.8–59.9) to 53.7 (95% CI: 50.0–57.4). However, in case of multiple TURBs, it was found that the initial impairment on mental health, gradually ameliorated. In terms of emotional role and physical and social functioning, a reduction on the estimated scores was confirmed at the 2nd or 3rd reoperation [17].

In our study, SF-36 physical health scores reached nadir at 6 months postoperatively, whereas the

Table 4
Internal consistency of the questionnaires' subscales using Cronbach Alpha

Subscale	Factor	Mauchly's Sphericity P	Interaction between Factor and Time P	Overall Effect of Factor P
SF-36 Physical	Treatment	**0.013**	0.216*	0.428
	Gender	**0.013**	0.558*	0.776
	Age	**0.002**	**0.011***	0.605
	Educational Level	**0.012**	0.222*	0.863
	Marital Status	**0.017**	0.754*	0.085
	Residence	**0.011**	0.479*	0.529
	Smoking	**0.003**	0.108*	0.419
	Alcohol	**0.012**	**0.015***	0.89
SF-36 Mental	Treatment	**0.023**	0.06*	0.83
	Gender	**0.009**	0.265*	0.379
	Age	**0.012**	0.241*	0.822
	Educational Level	**0.022**	0.237*	0.785
	Marital Status	**0.021**	0.502*	0.203
	Residence	**0.006**	0.291*	0.455
	Smoking	**0.007**	0.816*	0.641
	Alcohol	**0.006**	**0.02***	0.156
STAI-Y1	Treatment	0.051	0.059	0.253
	Gender	**0.016**	0.4*	0.872
	Age	**0.025**	0.84*	0.307
	Educational Level	**0.043**	0.811*	0.60
	Marital Status	**0.025**	0.758*	0.962
	Residence	**0.006**	0.117*	0.672
	Smoking	**0.027**	0.802*	0.707
	Alcohol	**0.017**	**0.011***	0.071
STAI-Y2	Treatment	0.305	0.157	0.798
	Gender	0.341	0.71	0.809
	Age	0.398	0.446	0.22
	Educational Level	0.398	0.229	0.763
	Marital Status	0.301	0.799	0.596
	Residence	0.291	0.377	0.346
	Smoking	0.516	0.202	0.828
	Alcohol	0.179	**0.003**	0.198

*Greenhouse-Geisser correction applied.

Table 5
Internal consistency of the questionnaires' subscales using Cronbach Alpha

Subscale	Time	Cronbach Alpha (%)
SF-36 Physical	2 weeks preoperatively	72.4
	3 months postoperatively	78.8
	6 months postoperatively	80.2
	12 months postoperatively	81.7
SF-36 Mental	2 weeks preoperatively	83.1
	3 months postoperatively	86.4
	6 months postoperatively	6.0
	12 months postoperatively	78.7
STAI-Y1	2 weeks preoperatively	88.6
	3 months postoperatively	93.7
	6 months postoperatively	92.8
	12 months postoperatively	35.0
STAI-Y2	2 weeks preoperatively	80.1
	3 months postoperatively	86.6
	6 months postoperatively	87.0
	12 months postoperatively	84.8

mental component was minimized at 3 months. A gradual improvement that reached higher values compared to the preoperative scores over the remaining follow-up period was identified in both tools. These findings are in contrast with the existing literature. In the BOXIT trial, patients with no NMIBC progression or recurrence reached a minimal EQ-5D score at 2 months postoperatively, with no further improvement [24]. Cases of grade III recurrence and progression were associated with statistically significant HRQoL decrease (–0.08; 95% confidence interval [CI], –0.13 to –0.03; and –0.10; 95% CI, –0.17 to –0.03, respectively).

Our data, also, suggested a significant association of age and alcohol with the Physical and Mental health, respectively. Similarly, in a study of 1160 BCs, Yu et al., reported an improved physical component in young and healthy, single males, that did not smoke and were diagnosed with a NMIBC. Moreover, gender, age, tumor stage and comorbidity status,

also, affected preoperative mental health. The biggest effect was found in the Physical Functioning domain, where a 10-year increase in age would decrease the score by 4 points. [3]. Although various patient characteristics interacted with time QoL measurements, none of them was an independent QoL affecting factor. Evidence from recent studies, though, suggest that postoperative HRQoL is significantly associated with modifiable behaviors such as physical activity, dietary habits and smoking. Sufficient physical activity, healthy diet, and non-smoking were significantly associated with HRQoL ($p < 0.001$) [7].

Likewise, anxiety levels are an important determinant of the treatment efficiency. Anxiety is defined as the unpleasant sense of fear in an unknown and ill-defined threat, followed by a variety of emotional and hemodynamic manifestations. Assessment of anxiety is based on the evaluation of both state and trait anxiety levels [18]. Preoperative anxiety is a well-documented entity with almost 80% incidence [25]. The physical and emotional distress symptoms have a wide severity range and can present several weeks preoperatively [26]. Furthermore, increased perioperative anxiety is related to suboptimal patient recovery, impaired immunologic function and increased morbidity and mortality. Despite initial diagnosis, socioeconomic factors, such as educational and marital status were predictive factors of preoperative anxiety. Preoperative distress, combined with postoperative pain and smoking are considered as independent postoperative anxiety risk predictors [27].

Regardless of a curative or a palliative approach, anxiety and depression rates in cancer patients are estimated at the level of 10% and 20%, respectively [28]. The significant association of BC diagnosis and management with anxiety is supported by the reported depression and anxiety rate. In a recent meta-analysis, pooled postoperative depression and anxiety rates ranged at the levels of 4.7–78% and 12.5–71.3%, respectively [29]. The long term duration of NMIBC treatment results to the development of post-traumatic stress disorder (PTSD) syndrome [30]. In this cohort, it was confirmed that uncertainty and PTSD symptoms were inversely related to QoL as it was quantified by the EORTC QLQ-30 and QLQ-NMIBC24. Although post-resection anxiety and depression status lessens gradually, tumor and operative characteristics, catheterization time and morbidity rates significantly affect overall distress levels. Our analyses showed a significant decrease of state anxiety, in contrast to the trait component, which remained stable. This could be attributed to the fact that since the patients were familiar to the follow-up process, they could more easily manage their reactions. These reactions though could not possibly alter their character and personal behavior in general. Both preoperative and postoperative STAI-Y scores were not associated to the study characteristics.

Another interesting fact in our study is that QoL and anxiety scores showed no statistically difference in terms of the preferred adjuvant therapy. Major concern for both epirubicin and BCG patients seemed to be the procedure itself (i.e, waiting, urethral catheterization, instillation, LUTS, etc) and not the recurrence or disease progress. There were no withdrawals due to LUTS or technical issues. Since they tolerated therapy well, all patients improved their scores over time.

Study limitations are the prospective methodology and non-randomization. Furthermore, there was no risk stratification of NMIBC patients (grade and staging) and no pre-cancer data on anxiety was collected. Additionally, no data on impact of financial/logistical constraints on QoL and anxiety were collected, even though this was not our aim. Although the statistical power of our findings was adequate, our sample size is relatively small. Finally, a longer follow up postoperatively period is needed to draw further conclusions regarding anxiety and QoL in patients with NMIBC.

In conclusion, an improvement in the Physical and Mental health aspect was identified during the follow-up period in patients receiving adjuvant bladder therapy for NMIBC. Furthermore, in contrast to Trait anxiety, State stress levels displayed a gradual declining trend. Preoperative Physical health was inversely correlated with age, while absence of alcohol was associated with lower Mental health. Overall, patient characteristics, habits and the administered treatment did not affect the postoperative QoL and anxiety. Due to several study limitations, larger scale studies with an extended follow up period are required for safe conclusions.

AUTHOR CONTRIBUTIONS

Alexandros Vaioulis: performance of work; writing the article. Konstantinos Bonotis: conception; performance of work. Konstantinos Perivoliotis: performance of work; interpretation or analysis of data. Yiannis Kiouvrekis: performance of work; interpretation or analysis of data; Stavros Gravas: performance of work. Vasilios Tzortzis: performance of work. Anastasios Karatzas: conception; performance of work; interpretation or analysis.

CONFLICT OF INTEREST

Alexandros Vaioulis has no conflict of interest to report. Konstantinos Bonotis has no conflict of interest to report. Konstantinos Perivoliotis has no conflict of interest to report. Yiannis Kiouvrekis has no conflict of interest to report. Stavros Gravas has no conflict of interest to report. Vasilios Tzortzis has no conflict of interest to report. Anastasios Karatzas has no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/BLC-201524.

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