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ORIGINAL ARTICLE

Quality of life deterioration and colorectal cancer staging in elderly patients. Which comes first?

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Summary

Purpose: *Never before the preoperative quality of life (QoL) score of colorectal cancer (CRC) patients was analyzed and linked directly to cancer staging according to pathology in specimens and, thereafter, in patients to estimate long-term prognosis. Our study attempted to give answers to these questions.*

Methods: *This was a prospective study of 80 elderly patients who underwent major colorectal surgery for cancer in a single University's surgical department conducted between 01/2018 and 12/2018. All patients aged >65 years, diagnosed with a resectable CRC without metastatic disease undergoing an elective surgery were prospectively included. As exclusion criteria were considered age <65 years, an emergency operation, non-resectable tumor, stage IV CRC and American Society of Anesthesiologists (ASA) score IV. All patients were asked to answer a self-administered questionnaire of the validated Greek version of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.*

Results: *Comparison of the mean score of EORTC QLQ-C30 showed stage I CRC was 87.62% (11.81%), 77.24% (12.91%) in stage II patients and 78.99% (15.25%) in stage III cancer. The mean difference between the three groups was statistically significant (p=0.002). Moreover, in post-hoc analysis, there was a statistically significant difference in the mean QLQ-C30 score between patients with stage I and stage II cancer (p=0.043) and between patients with stage I and stage III tumor (p=0.01), but this difference was not observed when comparing patients with stage II and III cancer (p=0.319).*

Conclusion: *Our study demonstrated a significant association between preoperative QoL and tumor staging as shown in the specimen's examination in elderly patients with CRC. More prospective studies are needed to elucidate how QoL and its fluctuations during the postoperative period can be correlated with long-term survival and disease progression in elderly CRC patients.*

Key words: *colorectal cancer, quality of life, Edmonton frail scale, Charlson score, elderly patients*

Introduction

The number of patients with cancer has increased in recent years with 18,1 million new cancer cases and 9,6 million cancer deaths estimated in 2018 worldwide. More specifically, colorectal cancer (CRC) is the third most commonly occurring cancer in men and the second most commonly occurring cancer in women [1]. While incidence rates for CRC have remained unchanged over the past two decades due to improvements in early detection and cancer treatment, 5-year survival is estimated more than 56% in Europe and 66% in the USA leading to a rising prevalence of patients with CRC [2].

Quality of life (QoL) is known to be an independent predictor of survival and response to ther-

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apy in cancer patients [3]. Braun et al found that a 10-point increase in baseline global QoL scores (using EORTC QLQ-C30) was associated with a 7% decreased risk of death in patients with CRC [4]. This result was also shown for other types of cancer [5]. Some authors proposed a theory according to which QoL could have a direct influence on tumor behavior and survival [6], while others suggested that QoL had a direct influence on therapy adherence and consequently on survival [7].

Long-term postoperative QoL among cancer patients is a subject of continuous research and debate with some authors suggesting that the stage and the site of CRC at diagnosis are major factors that define the QoL [3-5], as they determine symptoms, treatment and duration of therapy and on the other hand, some others fail to report any association between tumor stage and QoL. Moreover, psychological well-being and better QoL can improve the body's immune response and enhance resistance towards diseases. On the contrary, low QoL could deteriorate the immune response and subsequently speed up disease progression.

However, information on the prognostic significance of QoL tools used in patients with CRC does not exist. Additionally, never before the preoperative QoL of CRC patients was analyzed and linked directly to cancer staging according to the pathology specimens in patients to estimate long-term prognosis.

Methods

Patients

A prospective study of 80 elderly patients who underwent major colorectal surgery for cancer in a single University surgical department was conducted between 01/2018 and 12/2018. All patients aged>65 years, diagnosed with a resectable CRC without metastatic disease undergoing an elective surgery were included prospectively in the present study. As exclusion criteria were considered age <65 years old, an emergency operation, a non-resectable tumor, a stage IV CRC and American Society of Anesthesiologists (ASA) score IV.

Preoperatively, socio-demographic data and medical history were collected. The pathology records of the included patients were prospectively recorded in a database in order to identify the TNM stage.

Questionnaires and scores

Age-adjusted Charlson (AAC) Comorbidity Score, a modified version of Charlson Comorbidity Score considering age as one additional comorbidity index, was estimated preoperatively using the patients' medical records. This index consists of a weighted measure that incorporates age and 19 different medical categories weighted according to their impact on mortality. After taking into consideration all comorbidities with exception of the CRC, a total score was calculated [8].

In addition, Edmonton Frail Scale (EFS) was assessed as a baseline on admission by a trained researcher. Ten domains are tested in total, having a maximum score of 17 representing the highest level of frailty. Two performance-based items are used, the Clock test for cognitive impairment and the 'Timed Get Up and Go' for balance and mobility. The other domains tested include mood, functional independence, medication use, social support, nutrition, health attitudes, continence, burden of medical illness and QoL [9].

Moreover, all patients were asked to answer a self-administered questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [10].This questionnaire includes nine multi-item scales (five functional scales, three symptom scales and a global health and quality-of-life scale). The results of each score were estimated and recorded in a database with the respective patient's medical and pathology records.All patients answered the Greek validated version of the questionnaire [11].

Ethical considerations

Experimental therapeutic protocols were not applicable in this study. All data were analyzed anonymously using code numbers with respect to the patient's privacy and collected in the context of routine diagnostic and therapeutic procedures. Nevertheless, an informed written consent was obtained from every patient enrolled in the present study. The approval of the ethical committee of the hospital was obtained.

Statistics

The results were analyzed using GraphPad Prism 8.4.1 for Mac (GraphPad Software, San Diego, CA). Normal distribution of the data was evaluated by application of the D'Agostino and Pearson Omnibus normality test. Comparisons of the questionnaires regarding their effectiveness in patients with either stage I/II (early cancer) or stage III cancer were performed with two-tailed unpaired t-test for parametric data and Mann-Whitney U-test for nonparametric data. Comparisons of the qualitative variables were performed using chi square test. We also calculated the differences between the two groups, using the Hodges-Lehmann estimator. Differences were deemed significant with a $p \leq 0.05$.

Results

A total of 80 patients diagnosed with CRC were recruited in the present study; 52 (64.4%) were males and 28 (35.6%) females. The median age at diagnosis was 73 years (range: 65- 88). In 57 (71.2%) cases the tumor was located in the colon and in 23(28.8%) in the rectum. Twenty-nine patients (35%) had stage I disease in TNM staging, sixteen patients (20%) had stage II and thirty-four patients (45%) had stage III cancer at the time of diagnosis.

Table 1 shows the basic characteristics (age, gender, BMI, tumor's location, and surgical approach) classified by TNM stage. When comparing the main characteristics in each group, there was a statistically significant difference only between the mean age of patients in stage I and II and stage I and III. There was not statistically significant difference regarding the other parameters between the three groups, proving homogeneity.

The comparison of the mean scores in each calculated score is shown in Table 2. When comparing the (EORTC) QLQ-C30 scores, the mean score in patients with stage I cancer was 87.62% (11.81%), 77.24% (12.91%) in stage II patients and 78.99% (15.25%) in patients with stage III cancer. The mean difference between the three groups was statistically significant (p=0.002) (Figure 1). Moreover, in *post-hoc* analysis, there was a statistically significant difference in the mean QLQ-C30 score between patients with stage I and stage II cancer (p=0.043) and between the patients with stage I and stage III tumor (p=0.01), but this difference was not observed when comparing patients with stage II and III cancer (p=0.319).

Regarding AAC Charlson score, the mean score was 6.90 (1.38) in patients with stage I cancer, 6.50 (0.91) in stage II patients and 6.15 (1.43) in patients with stage III cancer, without statistically significant difference between the three groups (p=0.256). In addition, there was statistically significant difference between the groups (p=0.034) (Figure 1). The mean score in Edmonton Frail Scale was 3.90 (2.60) for the patients in stage I group, 5.58 (1.68) in stage II patients and 5.85 (2.84) in stage III group. More specifically, in *post-hoc* analysis, there was a statistically significant difference only between patients with stage I and stage III cancer (p=0.013), but there was no difference between patients in stage II and the other two groups (p=0.076 and p=0.770 respectively, Figure 1).

Limitations of the study

To the best of our knowledge, this is the first study associating preoperative patient's QoL and postoperative staging of CRC, although several limitations have to be considered when interpreting this study's outcomes. Data were collected from a single tertiary surgical department with a relatively similar population, thus the generalization is limited. Only elective colorectal operations by a certain group of surgeons were included resulting in possible selection bias. Moreover, the assessment of QoL was questionnaire-based and information bias may have occurred.

Discussion

The goal of this study was to evaluate any possible association between QoL and specimen cancer staging in elderly patients with colon cancer. We chose EORTC- QLQ C30 questionnaire as probably the most valid and reliable tool to assess the QoL among cancer patients. Simultaneously, other scales and scores were also used preoperatively and linked with the specimen staging. More specifically, Edmonton Frail Scale and Age adjusted Charlson score were also used as tools to evaluate any possible correlation with tumor staging.

Table 1. Basic characteristics

	Stage I	*Stage II*	*Stage III*	*p value*
Age, years, [mean (SD)]	71.05 (4.95)	76 (5.26)	75.42 (7.01)	0.025*
Male (n)	22	10	20	0.287‡
Female (n)	7	6	15	
BMI [mean (SD)]	25.67 (2.56)	25.08 (3.03)	23.88 (2.90)	0.097*
Colon (n)	19	12	26	0.693‡
Rectum (n)	10	4	9	
Open (n)	18	11	20	0.727‡
Laparoscopic (n)	11	5	15	

*ANOVA, ‡chi-square test

Table 2. Comparison of mean scores

Score/Stage	*Stage I*	*Stage II*	*Stage III*	*p value*
Preoperative QLQ [mean, SD)]	87.62% (11.81%)	77.24% (12.91%)	78.99% (15.25%)	0.002*
Edmonton frail scale [mean, SD)]	3.90 (2.60)	5.58 (1.68)	5.85 (2.84)	0.034*

*ANOVA

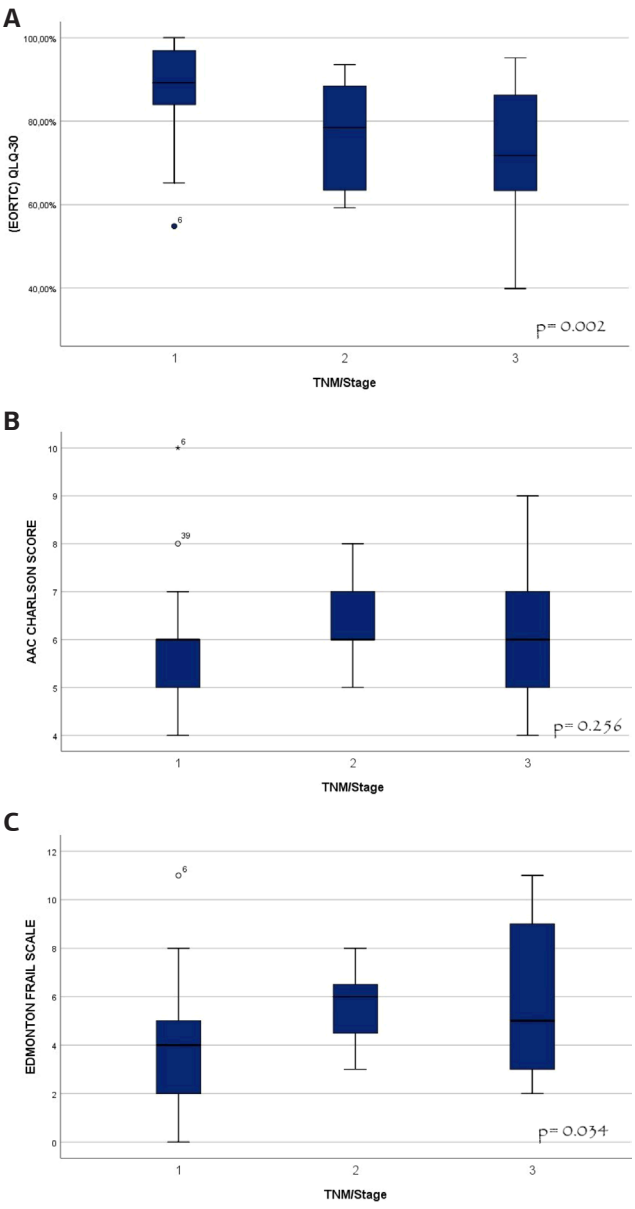

Figure 1. A: EORTC QLQ-30. **B:** Charlson score. **C:** Edmonton frail scale.

Interestingly, we found that when comparing the (EORTC) QLQ-C30 score, the mean score in patients with stage I cancer was 87.62%, in stage II cancer patients 77.24% and in patients with stage III cancer it was 78.99%. The mean difference between the three groups was statistically significant (p=0.002). Moreover, in *post-hoc* analysis, there was a statistically significant difference in the mean QLQ-C30 score between patients with stage I and stage II cancer (p=0.043) and between the patients with stage I and stage III tumor (p=0.01), but this difference was not observed between patients with stage II and III cancer (p=0.319). This could be interpreted that patient with early CRC (stage I) have a better QoL due to their early course in the disease that hasn't still affected their basic biological, health and physical function and activities explaining also probably their better survival rates comparing to stage II and stage III cancer patients [12].

On the other hand, regarding the preoperative QoL, until now, there was no evidence in the literature to explain whether lower overall QoL results in faster disease progression or whether the tumor biology is to blame for the QoL deterioration at the day of diagnosis. Several studies have reported the relationship between QoL and survival in patients with CRC and cancer in other sites of the body disclosing sometimes a strong correlation between those two variables [13-17]. Some subscales of QoL like baseline health and physical function were predictive of survival independent of the effects of tumor stage at diagnosis. Andreyev et al suggested that QoL had a direct influence on therapy adherence and consequently on survival [7].

Moreover, psychological well-being and better QoL can improve the body immune response and enhance resistance towards diseases. On the contrary, low QoL can deteriorate the immune response and resistance towards diseases and why not subsequently in cancer patients to speed up disease progression. Hui Zhu et al demonstrated in advanced CRC patients treated with dendritic cell vaccine and cytokine induced killer cell therapy induced an advanced immune response against CRC, improving QoL and prolonging overall survival [18]. Therefore, if postoperative QoL results, as it is already stated before, in better prognosis it could be a logical assumption that higher preoperative QoL also ameliorates the overall prognosis.

While these findings require further investigation in large patient cohorts, they may have important implications for patient stratification in clinical trials and aid in clinical decision-making. Additionally, psychological perioperative guidance and motivation is probably necessary to achieve high compliance to postoperative chemotherapy and subsequently better prognosis.

Similarly, when using Edmonton frail scale which assesses domains like mood, functional independence, medication use, social support, nutrition, health attitudes, continence, burden of medical illness and QoL, a statistically significant difference between the scores of stage I cancer patients and stage III (p=0.013) was demonstrated but with no difference between patients in stage II and the other two groups (p=0.076). Some domains assessed by this tool are the same with those tested in the QLQ questionnaire and that is probably the causal association between the above results. Regarding age-adjusted Charlson score, no differences were demonstrated between the groups, failing to

prove any possible association between patients' comorbidities and tumor staging.

Although our study raises interesting questions, several limitations require careful acknowledgment. The patient cohort was limited only in elderly patients with non-advanced CRC. Therefore, this sample cannot be representative for cancer patients in the general population. However, the study has several strengths, including no missing data on any QoL subscale for the entire study sample; a consistent population of elderly patients above 65 years old with non-metastatic CRC who underwent an elective surgery; the use of a valid and reliable QoL questionnaire; the availability of all clinical parameters in all individuals.

In summary, our study has demonstrated a significant association between preoperative QoL and tumor staging as shown in the specimen's examination in elderly patients with CRC. To the best of our knowledge, this is the first attempt to directly correlate QoL and tumor staging in non-metastatic CRC patients. More prospective studies are needed to elucidate how QoL and its fluctuations during the postoperative period can be correlated with long term survival and disease progression in elderly CRC patients.

Conflict of interests

The authors declare no conflict of interests.

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