

Original Article

Effect of oral nutritional supplementation on the post-discharge nutritional status and quality of life of gastrointestinal cancer patients after surgery: a multi-center study

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Background and Objectives: To evaluate the effect of oral nutritional supplementation (ONS) on the post-discharge nutritional status and quality of life (QoL) of gastrointestinal cancer patients after surgery. **Methods and Study Design:** A multi-center study was conducted on gastrointestinal cancer patients who received surgical treatment from 2013–2015. All patients were screened using the Nutrition Risk Screening 2002 (NRS 2002) to assess nutritional risk. Patients with nutritional risk were randomized into two groups: patients in the study group (n=55) were given dietary guidance and ONS, control group (n=59) received only dietary guidance. Anthropometric measurements, nutrition-related laboratory tests, and gastrointestinal function scores were also collected and analyzed using Student's t test and analysis of variance (ANOVA). In addition, the EQ-5D was used to evaluate patients' QoL. **Results:** Compared with baseline measurements, the body weight of patients in the study group increased by 1.35 ± 0.53 kg and 1.35 ± 0.73 kg at 60 and 90 days, which were significantly higher than those in the control group (-1.01 ± 0.54 kg, and -1.60 ± 0.81 kg at 60 and 90 days). The results from ANOVA showed that only weight and BMI differed significantly between the study and control groups and also between different measurement times ($p < 0.01$). No differences were found for the other indicators or QoL between the study groups. **Conclusions:** ONS may improve the weight and BMI of surgically treated gastrointestinal cancer patients post-discharge. However, these effects had little impact on patients' QoL.

Key Words: oral nutritional supplements, dietary guidance, postoperative gastrointestinal cancer

INTRODUCTION

Gastrointestinal cancer is a malignant disease that directly impacts the digestive tract and digestive subsidiary organs, including the stomach, bile duct system, pancreas, small intestine, colon, rectum, and anus. Treatment depends on the location of the tumor, the types of tumor cells present, and whether the cancer invades other tissues or has spread to other places. These factors also determine the prognosis and other physiological characteristics.

With the continued aging of the population in China, the incidence of gastrointestinal cancer is increasing too. Specifically, the risks of gastrointestinal cancer and related death in people over 75 years of age are 5-6 times and

7-8 times higher, respectively, than those in the general population.¹ Furthermore, 122.1 thousand and 78.2 thousand new cases of gastric and colorectal cancer are diagnosed every year in China, accounting for 42.73% and

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18.08% of cases worldwide in the same age groups, respectively.² The rise in the incidence of gastrointestinal cancer has been observed in other countries as well, especially in Asia in countries such as Iran, India, etc.³⁻⁵

Some dietary habits might account for the increase in gastrointestinal cancer in this area.³⁻⁵ Furthermore, gastrointestinal cancer might also directly trigger malnutrition through a direct influence on patients' gastrointestinal function. Hospitalized patients suffer from the effects of surgery, and related treatment measures such as fasting and bowel preparation may further affect their nutritional status. These factors combined with the quite limited hospital stay in China, which does not give patients enough time to completely recover, patients may still suffer from poor nutritional status at discharge. A study conducted in China showed that the incidence of nutritional risk and malnutrition is high in patients with malignant tumors when they are discharged from hospital,⁶ which could further lead to a myriad of negative consequences after discharge, including a decline in quality of life (QoL), an increased rate of readmission, and delayed administration of chemotherapy and radiotherapy if the malnutrition cannot be corrected in time.

However, from studies that only focus on a specific time, it is difficult to draw a strong conclusion, especially for the effects of 1-month interventions in the perioperative or postoperative periods.⁷⁻¹⁰ Studies of 3-month, long-term postoperative interventions for patients are lacking in China. Therefore, this multi-center study was designed to evaluate the effect of oral nutritional supplementation (ONS) on the nutritional status and QoL among patients discharged after surgical treatment for gastrointestinal cancer in China.

METHODS

Ethical statement

The study protocol was approved by the ethics committee of Beijing Hospital (Approval number: 2013BJYYec-046-02). Written informed consent was obtained from all patients or authorized relatives for those who were unable to communicate. The trial was registered in the Chinese Clinical Trial Register Center (No. ChiCTR-TRC-13003798).

Setting

This study was a prospective, multicenter, randomized study, which was led by Beijing Hospital. Another five hospitals including No. 3 Hospital of Peking University, Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Sixth People's Hospital Affiliated to Shanghai Jiaotong University, and Nanfang Hospital Affiliated to Southern Medical University participated in the study as centers.

Participants

During the period from June 2013 to August 2015, hospitalized patients with gastric or colorectal cancer to undergo radical surgery were included in this study. The inclusion criteria included: (1) no major complications after radical resection for gastrointestinal cancer; (2) age between 18–80 years; (3) a preoperative nutritional risk defined as NRS 2002 score ≥ 3 ; (4) Karnofsky score ≥ 70 and life expectancy > 6 months; (5) ability to tolerate

basic and normal diet or semi-liquid diets; (6) normal liver and renal function; (7) normal peripheral blood test results; and (8) provision of written informed consent. The exclusion criteria included: (1) inability to eat by mouth when discharged; (2) no preoperative nutritional risk as defined by NRS 2002 score < 3 ; (3) not treated with surgery or palliative surgery for gastrointestinal cancer; (4) severe digestive tract disease after surgery, such as gastrointestinal fistula, intestinal obstruction, or hemorrhage of the digestive tract; (5) severe abnormal liver and kidney function (ALT, AST ≥ 2 times of the upper limit of normal, Cr $> 176 \mu\text{mol/L}$); (6) leukocyte count < 3000 , hemoglobin $< 100 \text{ g/L}$, platelet count < 80 million/L in peripheral blood; (7) severe heart disease, diabetes, high blood lipids, electrolyte disorders, or condition that researchers believe it makes the participant not suitable for participating in the study; (8) galactosemia, amino acid metabolism, or allergy to milk or soy protein; and (9) poor compliance and absence of signed informed consent.

Randomization

SAS 9.1 software (SAS Institute Cary, NC, USA) was applied to generate a random code, and packet cards were produced according to the random code and placed into an opaque envelope. The eligible patients were assigned to the study group or control group according to the card from the envelope at discharge, which was defined as the baseline in this study.

Interventions

The patients in control group received dietary guidance from a responsible doctor according to the patient's disease and diet. All the patients in the study group received ONS consisting of a whole protein formula (Ensure complete, Abbott Laboratories, Zwolle, The Netherlands) in addition to the dietary guidance given by a full-time physician. Specifically, the doctors gave the patients uniform nutrition education material and introduced dietary principles, as well as answered the patient's questions.

The ONS used by the study group was an Entero-protein Family Enteral Nutrition Powder, which consists of protein, fat, carbohydrates, vitamins, minerals and dietary fiber, and can be used as the sole source of food. The protein, fat and carbohydrate content values were 15.9 g/100 g, 14 g/100 g and 57.4 g/100 g, respectively.

To prepare 250 kcal serving, 200 ml warm water was poured into a cup and then 55.8 g (or 6 leveled spoons of powder) were gradually mixed in, with slow stirring until the powder was fully dissolved. The patients in the study group received 500 kcal every day in three meals (About 167 ml / time for 10 am, 3 pm, and 8 pm) from the first day after discharge until 90 days.

Quality control

A follow-up physician was responsible for giving products, recycling cans and keeping the daily diary records. Meanwhile, other methods were conducted to ensure patients' compliance including telephone follow-up (≥ 1 time /week), short message service (SMS) alerts (2 times/week) and outpatient follow-up (once/month).

Indicators

Anthropometric measurements, nutrition-related laboratory tests, infection and complications, gastrointestinal functional status, and QoL scores were collected at baseline and 30, 60, and 90 days after discharge.

Anthropometric measurements included body weight, upper arm circumference, triceps skinfold thickness and hand grip strength. Height was measured at 6 am with patients not wearing shoes, and the scale adjusted to ± 0.5 cm. Body weight was measured when patients were fasting and free of shoes with light clothing, and the scale was adjusted to ± 0.2 kg. The non-dominant hand was used for arm circumference measurement. The distance between the surface of the scapula acromion and the olecranon at the elbow was measured, and the midpoint was marked. For the measurement of calf circumference, patients sat relaxed on the left of the researcher or were standing upright with balanced distribution of body weight to both legs. Measurement was performed at the widest point, and repeated measurements above and below the above-mentioned location were done to ensure that the first measurement was the maximum value (accuracy to 0.1 cm). The hand grip strength of the dominant hand was measured two times using the CAMRY EH101 Grip (Xiangshan apparatus group Ltd., Guangzhou, China) (adjusted to ± 0.1 kg) in this study.

Nutrition-related laboratory examination included measurement of hemoglobin, serum albumin, pre-albumin, triglyceride and total cholesterol levels. Quality control was achieved using the Westgard rules, and the quality evaluation criteria were in accordance with the relevant provisions issued by the inspection center of the National Health and Family Planning Commission, People's Republic of China.

Infectious complications were defined as the appear-

ance of pathogens in an originally sterile organism and confirmed by pathogen culture, or the appearance of clinical signs related to infection and other evidence proved by iconography or hematology.

Gastrointestinal functional status and QoL measures were obtained through questionnaires, including the gastrointestinal function status scale and a QoL scale (EQ-5D).

Statistical analysis

SAS 9.1 software was used for data analysis. The *t* test (quantitative variables with normal distribution) or χ^2 test (qualitative variables) was used to compare the baseline data. Analysis of variance (ANOVA) was used to identify significant changes in the data for each indicator over the four measurement times, and the *F* value and *p* value for both ONS intervention, repeat measurements and their interaction were calculated using Pillai's Trace method, with adjustment by the Greenhouse-Geisser Epsilon method. The Bonferroni method was applied for correction in multiple comparisons. $p < 0.05$ was considered indicative of a significant difference.

RESULTS

A total of 140 patients were enrolled in the study. Six patients were removed from the study during follow-up due to poor compliance, and 20 patients were lost due to personal reasons. Finally, 114 patients completed this study, including 55 patients in the study group and 59 patients in the control group. The general information and clinical data of the patients at baseline are shown in Table 1. There were no significant differences in any indicators between the two groups ($p < 0.05$), which indicated that the patient groups were comparable at baseline in this study. No adverse events occurred in any of the groups.

Table 1. Patients' general information and clinical data at baseline

	Control group (n=59)	Study group (n=55)	t value / Chi square value	<i>p</i>
Age (y)	60.9 $\pm$ 11.1	58.0 $\pm$ 15.0	1.153	0.251
Gender			1.126	0.289
Male (n, %)	35 (63.6%)	43 (72.9%)		
Female (n, %)	20 (36.4%)	16 (27.1%)		
Disease			0.262	0.609
Gastric cancer (n, %)	10 (18.2%)	13 (22.0%)		
Colorectal cancer (n, %)	45 (91.8%)	46 (78.0%)		
Postoperative chemotherapy (yes/no)	40/15	45/14	0.188	0.664
Height (cm)	164 $\pm$ 7.79	166 $\pm$ 7.19	-1.831	0.070
Weight (kg)	61.5 $\pm$ 10.7	61.8 $\pm$ 11.5	-0.140	0.889
BMI (kg/m ²)	22.8 $\pm$ 3.33	22.2 $\pm$ 2.87	1.134	0.259
Upper-arm circumference (cm)	24.7 $\pm$ 4.37	25.2 $\pm$ 4.02	-0.550	0.584
Hand grip strength (kg)	26.7 $\pm$ 8.39	27.7 $\pm$ 9.72	-0.527	0.599
Triceps skinfold thickness (mm)	13.7 $\pm$ 6.30	12.2 $\pm$ 6.93	1.219	0.225
Red blood cell count (10 ⁹ /L)	4.28 $\pm$ 1.08	4.11 $\pm$ 0.57	1.054	0.294
White blood cell count (10 ⁹ /L)	7.27 $\pm$ 2.72	7.17 $\pm$ 2.56	0.199	0.843
Hemoglobin (g/L)	117 $\pm$ 19.0	115 $\pm$ 17.0	0.750	0.455
Plasma prealbumin (g/L)	0.18 $\pm$ 0.06	0.50 $\pm$ 2.45	-0.908	0.366
Albumin (g/L)	35.6 $\pm$ 4.23	35.0 $\pm$ 3.98	0.729	0.468
Postoperative hospital stay (d)	9.50 $\pm$ 2.5	10.1 $\pm$ 2.90	1.215	0.227
NRS 2002 score	3.38 $\pm$ 0.56	3.530 $\pm$ 0.75	-1.162	0.248
EQ-5D score	77.2 $\pm$ 10.4	79.0 $\pm$ 9.72	-1.003	0.318
Gastrointestinal function	4.75 $\pm$ 3.13	4.80 $\pm$ 2.71	-0.093	0.926

BMI: body mass index; NRS 2002: nutritional risk screening 2002; EQ-5D: EuroQol five dimensions questionnaire.

Table 2. Changes in anthropometric indicators from baseline to 90 days post-discharge

	Time	Control group (n=59)	Study group (n=55)	t value	p
Weight (kg)	30d	-0.62±0.49	0.04±0.47	-0.974	0.333
	60d	-1.01±0.54	1.34±0.53	-3.103	0.003
	90d	-1.59±0.81	1.35±0.73	-2.705	0.008
BMI (kg/m ²)	30d	-0.36±0.22	0.03±0.21	-1.266	0.208
	60d	-0.43±0.22	0.49±0.21	-2.964	0.004
	90d	-0.44±0.23	0.54±0.22	-3.086	0.002
Upper-arm circumference (cm)	30d	-0.05±0.32	-0.01±0.31	-0.091	0.928
	60d	-0.59±0.32	-0.09±0.31	-1.087	0.279
	90d	-0.32±0.34	0.07±0.32	-0.830	0.408
Hand grip strength (kg)	30d	0.57±0.69	0.91±0.67	-0.350	0.727
	60d	-0.03±0.69	1.64±0.67	-1.732	0.086
	90d	0.14±0.72	1.63±0.68	-1.492	0.138
Triceps skinfold thickness (cm)	30d	-0.11±0.90	0.72±0.87	-0.657	0.512
	60d	0.28±0.90	-0.18±0.88	0.366	0.715
	90d	-0.16±0.94	-0.14±0.89	-0.020	0.984

Anthropometric indicators

Anthropometric indicators for patients in the two groups were measured at 30, 60, and 90 days after discharge, and the changes in these indicators from the baseline values are shown in Table 2. The ANOVA results showed that both ONS and four-time QoL measurements contributed to the significantly greater changes in body weight and BMI of patients in the study group compared with the control group at 60 and 90 days ($p<0.05$). However, the ANOVA showed that the effect of treatment and time of measurements had no significant effect on upper arm circumference, grip strength, or triceps skinfold thickness ($p>0.05$; Table 3).

Nutrition-related laboratory tests

Laboratory tests were conducted at 30, 60, and 90 days post-discharge, and the changes in measurements are shown in Table 4. The results of ANOVA showed that the effect of treatment and time of measurements had no significant effects in terms of the nutrition-related laboratory indicators ($p>0.05$).

Clinical outcomes

No infections or other complications were reported among the patients in the two groups during the study. The scores for gastrointestinal status and QoL are shown in Table 5, and the results in Table 3 showed that both ONS, 4-time QoL measurements and their interaction term had no effect on the nutrition-related laboratory indicators ($p>0.05$).

DISCUSSION

Gastrointestinal cancer is one of the most common malignancies encountered in clinical practice, and the incidence of nutritional risk at admission is as high as 65%.¹¹ Another study done by our team showed that the incidence rates for nutritional risk in surgical patients with gastric cancer and colorectal cancer were 40.3% and 32.9%, respectively.¹² Radical resection is an effective treatment with extensive resection of primary tumors, together with effective treatment for surrounding lymph node metastases. However, radical resection, especially with severe complications after surgery, can cause eating

difficulties, trauma and infection, etc., which might lead to increased catabolism and then deterioration in the nutritional status of patients. Combined with the inspection and treatment-related fasting during hospitalization, patients' digestive function and nutritional status may be further diminished.

In addition, Sanli et al found that the incidence of at least one gastrointestinal symptom in gastrointestinal cancer patients was 93.4% at discharge, which was much higher than that at admission (76.2%). Moreover, <36% of patients could tolerate semi-solid food and 63.4% of the patients were fed with fluids at discharge,¹³ which suggests that the nutritional intake was insufficient for these patients. Another study to evaluate the postoperative nutritional status of patients with gastric cancer showed that that patients' body weight decreased significantly and the proportion of high nutritional risk increased during 6 months after surgery.¹⁴ A systematic review including 3527 patients undergoing abdominal surgery confirmed that nutritional risk was associated with patients' poor clinical outcomes.¹⁵ Bin et al. found that nutritional support (especially enteral nutrition) can significantly reduce the rates of complications and infection in patients with nutritional risk.¹⁶ Another study showed that active nutrition intervention can reduce the risk of complications and 6-month re-admission rate in patients with nutritional risk.¹⁴

In this study, 500 kcal/d of ONS was given to patients as an intervention on the basis of dietary guidance, which not only fit the physiological characteristics of patients with gastrointestinal cancer, but also met the recommendations of Chinese guideline.¹⁷ Similar to a study completed in India in 2014,¹⁸ our results showed that patients who received ONS consecutively for 60 and 90 days had significantly smaller reductions in BMI and weight than patients in the control group who received only dietary guidance. Furthermore, a prospective, randomized, controlled trial study also found that patients might suffer from a decline in nutritional status after discharge and postoperative nutritional supplementation improved nutritional status,¹⁹ which was in line with the results of our present study. However, there were no differences in the changes in upper arm circumference, grip strength, plas-

Table 3. ANOVA results for the contribution of ONS, four-times QoL measurements and the interactions

	ONS		QoL measurements		ONS x QoL measurements		QoL measurements		ONS x QoL measurements	
	F(P-T)	p	F(P-T)	p	F(P-T)	p	F(G-G)	p	F(G-G)	p
Weight (kg)	8.31	<0.0001*	9.72	<0.0001*	7.92	<0.0001*	9.25	<0.0001*	7.82	<0.0001*
BMI (kg/m ²)	7.96	<0.0001*	9.28	<0.0001*	8.41	<0.0001*	9.09	<0.0001*	7.95	<0.0001*
Upper-arm circumference (cm)	0.93	0.340	5.33	0.137	0.14	0.874	4.47	0.230	0.11	0.885
Hand grip strength (kg)	0.46	0.502	1.09	0.470	0.66	0.029	1.55	0.343	0.44	0.622
Triceps skinfold thickness (cm)	0.55	0.464	0.39	0.681	0.32	0.731	0.16	0.782	0.15	0.791
HGB (g/L)	0.01	0.961	40.5	0.000	0.95	0.060	0.01	0.961	0.81	0.463
PA (g/L)	2.83	0.101	1.11	0.357	0.91	0.447	0.39	0.696	0.30	0.765
ALB (g/L)	1.79	0.188	1.19	0.755	1.47	0.237	38.3	0.000	1.18	0.319
TC (mmol/L)	2.32	0.135	0.17	0.907	0.14	0.706	0.31	0.576	0.16	0.171
TG (mmol/L)	3.95	0.054	4.31	0.110	0.28	0.839	4.07	0.010	0.33	0.784
Gastrointestinal status score	2.83	0.101	1.33	0.256	0.18	0.674	0.03	0.864	0.19	0.666
EQ-5D score	0.33	0.570	2.49	0.121	0.39	0.537	1.69	0.104	0.38	0.526

ONS: oral nutritional supplementation; QoL: quality of life; F(P-T): F-value calculated by Pillai's Trace method in multivariate analysis; F(G-G): F-value corrected for the degree of freedom of variants using Greenhouse-Geisser Epsilon method.

* $p < 0.01$

Table 4. Measurements from nutrition-related laboratory tests

	Time	Control group (n=59)	Study group (n=55)	t value	p
HGB (g/L)	30d	7.18±2.09	8.11±2.03	-0.320	0.749
	60d	10.0±2.10	12.3±2.03	-0.767	0.445
	90d	9.09±2.18	12.2±2.06	-1.037	0.302
PA (g/L)	30d	0.05±0.15	0.32±0.14	-1.295	0.198
	60d	0.05±0.15	0.23±0.14	-0.832	0.407
	90d	0.08±0.15	0.20±0.14	-0.579	0.564
ALB (g/L)	30d	5.92±0.70	5.38±0.68	0.546	0.586
	60d	5.99±0.72	6.19±0.69	-0.208	0.835
	90d	5.92±0.76	6.12±0.70	-0.197	0.844
TC (mmol/L)	30d	0.45±0.14	0.45±0.13	-0.026	0.979
	60d	0.68±0.15	0.57±0.14	0.552	0.582
	90d	0.71±0.16	0.573±0.14	0.647	0.518
TG (mmol/L)	30d	-0.20±0.12	-0.26±0.11	0.349	0.728
	60d	0.03±0.13	-0.12±0.12	0.873	0.384
	90d	0.09±0.14	-0.21±0.12	1.604	0.111

Table 5. Scores for gastrointestinal status and quality of life in the two groups

	Time	Control group (n=59)	Study group (n=55)	t value	p
Gastrointestinal status score	30d	-1.66±0.47	-2.01±0.46	0.535	0.594
	60d	-2.53±0.47	-3.40±0.46	1.328	0.187
	90d	-3.35±0.49	-3.75±0.46	0.586	0.559
EQ-5D score	30d	3.81±1.73	3.71±1.68	0.043	0.966
	60d	5.72±1.73	6.46±1.69	-0.308	0.759
	90d	9.76±1.79	8.49±1.70	0.517	0.606

ma albumin, gastrointestinal function, and QoL between the two groups.

Previous studies suggested that 12 weeks of enteral nutrition supplementation after surgery in malnourished patients can significantly improve their QoL.¹⁹ However, similar results were not observed in this study. The reasons may be as follows: 1) the EQ-5d scale has some subjectivity, as patients with a lower level of education may not fully understand the meaning of the EQ-5d scale, resulting in unreliable measurement results, and this study did not include the education level of the patients as an influencing factor among the observed indicators; 2) the EQ-5d is widely used to evaluate the health index and QoL in patients, but whether it can effectively reflect the QoL after gastrointestinal surgery remains to be explored; and 3) the sample size of this study was limited, and research with a larger sample size may be needed to confirm whether nutritional intervention can improve patients' QoL after gastrointestinal surgery.

The nutrition treatment guideline issued by the China Anti-Cancer Association for cancer patients recommends a five-level ladder treatment model for nutritional intervention in malnourished people, which includes dietary plus nutrition education as the first ladder; dietary plus oral nutritional supplementation as the second ladder; total enteral nutrition including oral and/or tube feeding as the third ladder; partial enteral nutrition plus partial parenteral nutrition as the fourth step; and total parenteral nutrition as the fifth step. The guideline recommends that the nutrition treatment should be upgraded to a higher level of the ladder when patients cannot meet 60% of the targeted energy requirements for 3-5 days.²⁰ In addition, "The expert consensus on adult ONS", which was released by the Chinese Society for Parenteral and Enteral Nutrition in 2017 indicated that ONS could increase the daily energy and protein intake and further improve the nutritional status, tissue function, and QoL for patients with tumors.²¹

According to the recommendations of the five-level ladder treatment model, oral nutritional supplement therapy is no doubt the preferred nutritional intervention for patients with gastrointestinal cancer, especially for outpatients receiving neoadjuvant chemotherapy. A systematic review by Baldwin et al. confirmed the effectiveness of ONS in cancer patients.²² Furthermore, a number of recent studies also confirmed other benefits of ONS, including reductions in weight loss and improvements in QoL and health economics indicators.²³⁻²⁵

The present study has some limitations. Firstly, it was a non-blinded, open-label study, and the design could cause a risk of bias in the process of the study procedures.

However, we implemented blinding for the assessor to minimize the risk of bias. Secondly, ensuring patients' compliance with the ONS is difficult due to the single taste and long period. However, a follow-up physician was appointed and responsible for giving products, recycling cans, and keeping daily records, and other communication methods including telephone, SMS alerts, and other means of contact were used to improve patients' compliance. Lastly, the sample size of this study might be too small to confirm the effects on QoL and other outcome indicators.

This study was the first randomized controlled clinical study of long-term ONS in China, and positive results for body weight and BMI were obtained. Although these findings are consistent with previous ONS studies, the results are of positive significance for guiding clinicians in China to apply this technology.

In conclusion, our study results indicate that ONS might improve the body weight and BMI of gastrointestinal cancer patients after surgical treatment. However, ONS did not lead to significant improvement in patients' QoL.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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